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ORIGINAL ARTICLES.

ON THE INHERITANCE OF DIABETES MELLITUS.

I. AN ANALYSIS OF 675 FAMILY HISTORIES.*

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THE suggestion has been made that the potentiality for developing diabetes may be inherited as a simple Mendelian recessive (White¹). No definitive conclusions were possible, however, because the data in the instance cited were deficient in certain information and no control population was available. We have accordingly collected the family histories of 523[†] diabetic patients appearing at the Joslin Diabetic Unit from July, 1932, to October, 1932, and control histories were obtained from 153 non-diabetic patients.

The data were collected by questioning the patient, and in a large number of cases at least one near relative. Recording was made of all facts that appeared to be pertinent for this or succeeding

* Since this manuscript was received, an article by William Allan, on Heredity in Diabetes, has appeared in the *Annals of Internal Medicine* (1933, 6, 1272) reiterating Dr. White's suggestion that potentiality of diabetes may be transmitted as a recessive unit character. We are glad that his suggestion that a genetic study be carried out on less meager data than he was able to collect can be so promptly met.—EDITOR'S NOTE.

[†] Actually 531 successive cases were recorded; 8 were discarded because of inadequate or faulty recording.

surveys, and a card was made out for each patient, as presented in Fig. 1. These records were obtained in part from patients returning for periodic examinations and whose family histories were already somewhat known, and in part from patients appearing for the first time. In the case of the former group previous records provided a check on the accuracy of the histories. We were especially particular to obtain the correct age of all living siblings and parents and the age at death of all dead siblings and parents, for, as our later analysis will show, any detailed treatment must be based on the division of these relatives into certain age groups.

FIG. 1.—THE CASE RECORD OF EACH DIABETIC PATIENT.

Patient.					Siblings.						
Case No.	Sex.	Date of personal observation.	Onset age.	Duration of diabetes.	Present age.	Present age.		Age at death.	Onset age.	Duration of diabetes.	Fatal date.
						Males.	Females.				
Mother.					Father.						
Present age.	Age at death.	Onset age.	Duration of diabetes.	Fatal date.	Present age.	Age at death.	Onset age.	Duration of diabetes.	Fatal date.		
Spouse.		Children.		Spouse and children.							
Present age.	Age at death.	Present age.	Age at death.	Onset age.	Duration of diabetes.	Fatal date.	Other diabetic relatives.		Remarks.		

In Table 1 we have assembled the incidence data by decades for our control and for our diabetic populations. We have compared the incidence in the parents and siblings of each patient because these are the most accurately recorded. Data on other relatives are much less reliable and their significance more obscure. The crude figures are as follows: in 523 diabetic families there were reported 187 diabetic relatives other than parents and siblings in 110 families, or 22.94 per cent of the families with diabetic blood relatives; in the 153 non-diabetic families 16 families or 10.46 per cent reported 21 blood relatives with diabetes. The difference between the incidences among these relatives in the two groups is therefore 12.48 per cent; the probable error of this difference is 2.08 per cent, and the difference divided by the probable error is 6. The odds are 19,300 to 1 against such a difference having arisen as a result of chance alone. We may, therefore, say that there has been reported in our diabetic families a significant excess of families with diabetic blood relatives (other than parents and siblings) as compared with the control families.

A similar excess of diabetic siblings and parents is apparent on inspection of Table 1. It will be noted that our control population contains, particularly among the siblings, relatively more persons in the early decades than does the diabetic population. The proper comparisons must therefore be made between the same decades and

not for the whole population, since diabetes incidence changes from decade to decade, rising to a maximum at middle age and then declining. In this and in all succeeding tables the age at death of dead persons has been taken at present age; obviously the opportunity for developing diabetes is limited to the years during which an individual is alive.

TABLE 1.—COMPARATIVE INCIDENCE OF DIABETES IN PARENTS AND SIBLINGS OF A CONTROL AND A "DIABETIC" POPULATION.*

Decade.	"Diabetic" population.			Control population.			"Diabetic" population.			Control population.		
	Dia-betic par-ents.	Non-dia-betic par-ents.	Per cent dia-betic.	Dia-betic par-ents.	Non-dia-betic par-ents.	Per cent dia-betic.	Dia-betic sib-lings.	Non-dia-betic sib-lings.	Per cent dia-betic.	Dia-betic sib-lings.	Non-dia-betic sib-lings.	Per cent dia-betic.
1	4	243	1.46	0	90	0.0
2	7	141	4.73	1	90	1.11
3	0	16	0.0	0	6	0.0	3	216	1.37	0	120	0.0
4	4	119	3.25	0	14	0.0	7	207	3.27	1	101	0.96
5	6	134	4.29	0	54	0.0	11	259	4.07	0	94	0.0
6	20	153	11.56	1	76	1.39	26	319	6.96	0	77	0.0
7	32	194	14.16	2	62	3.23	32	224	12.50	2	44	4.55
8	18	180	9.09	3	56	5.35	10	92	9.80	0	23	0.0
9	5	121	3.97	0	29	0.0	0	8	0.0	0	5	0.0
10	1	29	8.33	0	3	0.0						
Totals	86	946	8.33	6	300	1.96	100	1709	5.85	4	647	0.62

* Several parents in each group whose ages were unknown have been omitted from this table.

A cursory inspection of Table 1 reveals that in every decade excepting the 3d in the parent population and the 9th in the sibling population, the diabetes incidence in the control group is on a percentage basis *less* than in the diabetic group, and in the two exceptional decades the incidence is the same, *i. e.*, 0.0 per cent. Now if the two populations were not significantly different as regards the incidence of diabetes we would expect the relative percentage of diabetics in each decade to fluctuate, to be higher now in one population, now in the other. The probability that in any decade one population will show a lesser incidence than the other is of course $\frac{1}{2}$, and the probability of an equal or higher incidence is also $\frac{1}{2}$. We can calculate the probability that in the 17 decades recorded (*i. e.*, 8 among the parents and 9 among the siblings) only 2 should show an equal (or greater) incidence in the control population, by the theorem which states that

$$P_m(n) = C_n^m p^n (1-p)^{m-n} \quad (1)$$

where P is the probability we are seeking, m the number of trials, *i. e.*, the total number of decades, n the number of times that an equal or greater incidence occurs, and p the chances of occurrence. This becomes then

$$\begin{aligned} P_m(n) &= C_2^{17} (0.5)^2 \times (0.5)^{15} \\ &= 136 \times 0.25 \times 0.00003055 \\ &= 0.001038 \end{aligned}$$

The consistent lesser incidence of diabetics *per* decade in the control population could thus arise by chance alone once in 1000 trials. As we shall examine into the probability of various incidences hereafter, it may be well to state now that a value of P below 0.01 in the type of instance we shall examine is ordinarily taken to indicate a statistically significant deviation from random occurrence.

Our first examination, then, leads to the conclusion that there is a statistically significant excess of diabetic parents and siblings in our diabetic population as compared with the control population. We may proceed to determine the statistical significance of the difference in incidence in the 2 groups of parents and the 2 groups of siblings separately by the use of the χ^2 method. We are now interested, essentially, in determining the independence of our two populations and not in explaining this presumed independence. Accordingly we can calculate an "expected" incidence of diabetics for each decade by taking the known total number of diabetics and non-diabetics and allocating them in proportion to the total number of individuals in that decade in each population. This involves the calculation of expectancy for each decade of a 2 by 2 classification of the type described by Fisher² (pp. 85 and ff.). The expected values so calculated are listed in Table 2. The value of $\chi^2 = 18.366$ for the parents gives a probability of 0.0095, the $\chi^2 = 22.153$ gives for the siblings a probability of 0.0047, and each of these probabilities indicates a significant excess of diabetics in the diabetic populations.

The determination that we have presented of a statistically significant excess of diabetic relatives in the families of diabetic patients affords, of course, no hypothesis to account for the excess. If diabetes were an infectious disease we might advance the notion that a greater liability to infection exists in the families of the diabetic patients. Or we might suppose that a certain dietary régime leading to the eventual manifestation of diabetes is characteristic of diabetic families. We propose, however, to examine the hypothesis that the potentiality for developing diabetes is inherited as a simple Mendelian recessive, so that all persons capable of developing diabetes may be designated as mm . Non-diabetics are either MM or Mm . Only three types of matings can produce mm offspring. These are:

- (1) $Mm \times Mm = 1 MM : 2 Mm : 1 mm$
- (2) $Mm \times mm = 1 Mm : 1 mm$
- (3) $mm \times mm = 1 mm$

Accordingly we may classify our families at once into these 3 groups: (1) both parents non-diabetic, (2) one parent diabetic, (3) both parents diabetic. In the last group we have 2 (possibly 3) matings, and except to mention now that the occurrence of diabetes in the offspring is not inconsistent with our Mendelian hypothesis we

TABLE 2.—COMPARISON OF OBSERVED AND "EXPECTED" INCIDENCE IN A CONTROL AND A "DIABETIC" POPULATION.

Decade.	"Diabetic" population.				Control population.				"Diabetic" population.				Control population.				Deviation.
	Diabetic parents, observed.	Non-diabetic parents, observed.	Diabetic parents, expected.	Non-diabetic parents, expected.	Diabetic parents, observed.	Non-diabetic parents, expected.	Diabetic parents, expected.	Non-diabetic parents, expected.	Diabetic siblings, observed.	Non-diabetic siblings, observed.	Diabetic siblings, expected.	Non-diabetic siblings, expected.	Diabetic siblings, observed.	Non-diabetic siblings, observed.	Diabetic siblings, expected.	Non-diabetic siblings, expected.	
1	0	90	1.07	88.93	1.07
2	7	141	4.95	143.05	1	90	3.05	87.95	2.05
3	0	119	3.59	119.41	0	0	0.0	6.00	3	216	1.94	217.06	0	120	1.06	118.94	1.06
4	4	134	4.33	135.67	0	54	1.67	52.33	7	207	5.37	208.63	1	104	2.63	102.37	1.63
5	20	153	14.53	158.47	1	76	6.47	70.53	11	259	8.16	261.84	0	94	2.84	91.16	2.84
6	32	194	26.50	199.50	2	62	7.50	56.50	26	319	21.26	323.74	0	77	4.74	72.26	4.74
7	18	180	16.18	181.82	3	56	4.82	54.18	32	224	28.82	227.18	2	44	5.18	40.82	3.18
8	5	121	4.06	121.94	0	29	0.94	28.06	10	92	8.16	93.84	0	23	1.84	21.16	1.84
9	1	29	0.91	29.09	0	3	0.09	2.91	0	8	0.0	8.00	0	5	0.0	5.00	0.0
10	1	29	0.91	29.09	0	3	0.09	2.91	0	8	0.0	8.00	0	5	0.0	5.00	0.0
Totals	86	946	70.10	961.90	6	300	21.90	284.10	15.90	100	1709	81.59	1727.41	647	22.41	628.59	18.41

$$\chi^2 = 18.366$$

$$P = 0.0095$$

$$\chi^2 = 22.153$$

$$P = 0.0047$$

shall omit them from further consideration. In the first group we have 440 families, and in the second 81 families.

The reasons why we at once entertain this hypothesis rather than the hypothesis of dominance are: (1) The genealogies that we have available indicate that the disease may skip one or more generations, and the genealogies in the literature generally support this notion (see Baur, Fischer, and Lenz,³ pp. 352-354 and the discussion of the literature in this paper); (2) on an hypothesis of dominance at least one parent in each mating should be diabetic or potentially diabetic. When one considers the ages of these parents and the ordinary age-incidence relations of diabetes the percentage of diabetic parents is much too small to admit an hypothesis of dominance except on special assumptions.

Omitting for the moment any discussion of the possibility that some of the parents classed as Mm are genetically mm , let us see how the incidence of diabetes among the children accords with the Mendelian expectation.

Since each of the families was chosen because at least one diabetic child had been identified, the Mendelian expectation of mm among the children becomes: $\frac{p}{1 - (q)n}$, where p is the probability of an mm individual appearing, q the probability of an mm individual not appearing, and n is the number of children *per* family. Thus, in a cross of $Mm \times Mm$ where we have one diabetic patient and 5 siblings the expectation of mm individuals is:

$$\frac{1/4}{1 - (3/4)^6} = 30.41 \text{ per cent}$$

We actually have 38 families of 6 children each in our $Mm \times Mm$ cross. Of the 228 children we would expect 30.41 per cent or 69.33 to be mm . We have actually identified 38 of these as patients so that we would expect 31.33 mm individuals among the siblings. These expected mm individuals should be distributed among the various decades in proportion to the total number of persons in each decade; thus in the 1st decade there are 23 of these siblings or 12.11 per cent; accordingly we would expect 12.11 per cent of 31.33 or 3.79 mm individuals in the 1st decade. Applying these methods throughout, we can calculate the expectation of mm individuals for each decade in all the various-sized families, and by collecting the data arrive at an expectation *per* decade for the whole population of siblings in each of the two crosses. The patients are omitted from our tabulations and subsequent calculations since they serve merely to bring a given family into our tables.

The expected numbers of mm individuals do not represent actual diabetics, but only persons capable of developing diabetes. To calculate the actual number of mm individuals identifiable as diabetics we must have recourse to the age-incidence tables. Our final calculations depend upon one major assumption, namely, that

potential diabetics before they develop diabetes are subject to the same chances of death as are other members of the general population. If this be granted as a reasonable assumption, and there is no very definite evidence to the contrary, we can calculate from the ordinary life tables and the tables giving the age-incidence relations of diabetes, the proportion of potential to identifiable diabetics for each decade. This has been done in Table 3, using Glover's tables* for the 1910 population of the United States, and diabetes incidence data from three sources: (1) The first 6000 cases of Dr. Elliott P. Joslin; (2) the data of Adams⁴ and (3) the actual incidence among the patients used in this study. The first group of cases were assembled between 1898 and 1926, and the life tables of the year 1910 are perhaps justifiably applicable to them. The data of Adams were collected at the Mayo Clinic and may be taken to apply fairly generally. The incidence data for this population are employed for reasons which will be given later.

TABLE 3.—AGE INCIDENCE AND POTENTIAL DIABETICS.

Decade.	Per cent surviving (Glover, 1910).	Per cent diabetics ap- pearing among all identified (Joslin).	Relative number of potential diabetics.	Total potential and diabetic.	Per cent identified.	Incidence data (Adams).	Total potential and diabetic.	Per cent identified.	Incidence data (this population).	Total potential and diabetic.	Per cent identified
1 . . .	82.46	4.57	165.49	170.06	2.69	4.3	168.78	2.55	8.65	164.28	5.27
2 . . .	97.11	6.52	154.19	160.71	4.06	6.1	159.73	3.82	12.88	151.13	8.52
3 . . .	94.64	8.09	137.84	145.93	5.54	9.5	145.40	6.53	9.62	130.84	7.35
4 . . .	92.43	12.94	114.47	127.41	10.16	12.3	125.61	9.79	9.81	112.04	8.76
5 . . .	89.18	23.70	78.38	102.08	23.22	19.7	101.05	19.50	18.46	91.17	20.25
6 . . .	81.87	27.18	36.99	64.17	42.36	27.4	66.60	41.14	24.04	59.53	40.38
7 . . .	66.13	13.73	10.73	24.46	56.13	18.2	25.92	70.22	13.85	23.47	59.01
8 . . .	40.55	3.10	1.25	4.35	71.26	2.4	3.13	76.68	2.50	3.90	64.10
9 . . .	13.62	0.17	0.0	0.17	100.00	0.1	0.10	100.00	0.19	0.19	100.00

The relative numbers of potential diabetics are determined from Glover's survival data as follows: In decade 9, 0.17 diabetics *per* 100 appear (Table 3, column 2). These represent 13.62 per cent of the persons alive in the previous decade (Table 3, column 1) who were capable of developing diabetes, but were not identified. Since $0.17 = 13.62$ per cent, $1.25 = 100$ per cent, *i. e.*, 1.25 potential diabetics (Table 3, column 3). These 1.25 potential diabetics, plus the 3.10 identified diabetics give 4.35 individuals in the 8th decade (Table 3, column 4) who, on our hypothesis, are all *mm*. The number of potential diabetics required to produce these 4.35 individuals is again calculated from the general survival data, and so on for each decade.

* Strictly, these tables should be corrected for the contribution of diabetes to each decade as a cause of death. Such correction is unnecessary in view of the slight alteration that would ensue.

It will be seen from an inspection of Table 3 that the computations derived from these various sources agree fairly well. We have in addition used the age-incidence data for Dr. Joslin's last 4000 cases, and for cases 7001 to 8000, and find no noteworthy differences between these incidence data and those presented in Table 3. We have also employed the Massachusetts life tables for 1900 in calculations with Dr. Joslin's data, since a good number of his cases were assembled from Massachusetts. These calculations are not presented as they do not differ significantly from the figures obtained by the use of Glover's tables.*

TABLE 4.—THE EXPECTED AND OBSERVED INCIDENCES OF DIABETICS IN THE SIBLINGS OF PATIENTS WITH BOTH PARENTS NON-DIABETIC (I. E., $Mm \times Mm$).

Decade.	Potential diabetics expected.	Per cent identifiable (Joslin, U. S. A.).	Number identifiable.	Number observed.	Total number of siblings.	Number identifiable (Adams, U. S. A.).	Number identifiable (this population, U. S. A.).
1	34.74	2.69	0.93	3	209	0.88	1.83
2	21.59	4.06	0.88	6	134	0.82	1.84
3	32.41	5.54	1.80	1	196	2.12	2.38
4	28.15	10.16	2.86	6	168	2.76	2.47
5	35.44	23.22	8.23	7	210	6.91	7.18
6	46.81	42.36	19.83	14	281	19.26	18.90
7	33.19	56.13	18.63	20	201	23.31	19.59
8	14.31	71.26	10.20	7	88	10.97	9.17
9	1.32	100.00	1.32	0	8	1.32	1.32
Totals	247.96	64.68	64	1495	68.35	64.68
Deviation	0.68	4.35	0.68
Probable error	± 5.31	± 5.45	± 5.31
Deviation	0.13	0.80	0.13
Probable error	0.13	0.80	0.13

We may now calculate the expected number of mm individuals in each decade actually identifiable as diabetics by multiplying the Mendelian expectation by the expectation of identification. Thus in the cross $Mm \times Mm$ in the first decade we expect 34.74 mm individuals (Table 4, column 2). On the basis of Joslin's tables 2.69 per cent of these or 0.93 individuals should be identified as diabetics. The observed and expected numbers of diabetics *per* decade calculated in this way are presented in Tables 4 and 5 for the crosses $Mm \times Mm$ and $Mm \times mm$ respectively. The totals agree remarkably well, in fact somewhat better than one would expect by chance alone regardless of the source of the incidence data. But when the

* One might conceivably employ a life table constructed from the data of this population itself, but such a procedure is open to numerous objections, *e. g.*, the probability of high infant mortality in children of diabetic mothers, the debatable question of the inclusion of the parents, and the obvious limitations of a relatively small population.

data are examined decade by decade it is at once obvious that there is an excess of diabetics in the first few decades when we derive our expectations from Joslin's or Adams' data. It happens that we have in our population a larger proportion of younger patients than ordinarily appear in diabetic populations generally. If there were a positive correlation between the ages of onset of diabetes in siblings, then we would expect such an excess of diabetics in the earlier decades. For that reason we have employed the incidence data of this population in calculating the proportions of identifiable diabetics (see Table 3, last 3 columns, and the last columns of Tables 4 and 5). Actually, we do find that employing the diabetes incidence among the patients of this population better meets the expectation for the earlier decades than do the more general data of Joslin or Adams.

TABLE 5.—THE EXPECTED AND OBSERVED INCIDENCES OF DIABETICS IN SIBLINGS OF PATIENTS WITH 1 DIABETIC PARENT (I. E., $Mm \times Mm$).

Decade.	Potential diabetics expected.	Number identifiable (Joslin).	Number observed.	Total number siblings.	Number identifiable (Adams).	Number identifiable (this population).
1	15.83	0.43	1	38	0.40	0.83
2	5.58	0.23	1	14	0.21	0.48
3	9.50	0.53	2	23	0.34	0.70
4	18.32	1.86	1	46	1.79	1.60
5	23.32	5.41	3	58	4.55	4.72
6	25.39	10.76	12	62	10.45	10.25
7	18.66	10.47	9	47	13.10	11.01
8	4.43	3.16	3	11	3.40	2.84
Totals	131.03	32.85	32	299	34.24	32.43
Deviation	0.85	2.24	0.43
Probable error	± 3.65	± 3.71	± 3.63
Deviation						
Probable error	0.23	0.60	0.12

For testing the agreement between expectation and observation in each decade we have computed the probabilities of agreement from the formula

$$P = (p)^D \times (q)^R \times \frac{|n|}{|D| |R|}$$

Where D is number of non-diabetics observed, p the expectation of non-diabetics, R the number of diabetics observed, q the expectation of diabetics, and n the total number of individuals observed. This formula is particularly applicable to ratios involving small numbers (see Warwick⁵). The values of P per decade for $Mm \times Mm$ and $Mm \times mm$ combined are given in Table 6. Since any value of P below 0.01 may be taken as showing a significant deviation

from expectation, it will be noted that only in the second decade is there any significant departure from expectation. This is not surprising when we consider that a disproportionate number of diabetic patients in our population are present in that decade.

TABLE 6.—THE PROBABILITIES (P) OF THE OBSERVED RATIOS IN EACH DECADE CALCULATED ON THE BASIS OF THE EXPECTED RATIOS FOR THE CROSSES $Mm \times Mm$ AND $Mm \times mm$ COMBINED.

Decade.	No. of diabetic siblings observed.	Total number of siblings.	No. of diabetic siblings expected (Joslin).	P (Joslin).	No. of diabetic siblings expected (Adams).	P (Adams).	No. of diabetic siblings expected (this population).	P (this population).
1	4	247	1.36	0.0362	1.28	0.0319	2.66	0.1483
2	7	148	1.11	0.0001	1.03	0.0000	2.32	0.0066
3	3	219	2.33	0.2111	2.46	0.2245	3.08	0.1800
4	7	214	4.72	0.0922	4.55	0.0802	4.07	0.0636
5	10	268	13.64	0.0722	11.46	0.1137	11.90	0.1094
6	26	343	30.59	0.0534	29.71	0.0644	29.15	0.0658
7	29	248	29.10	0.0781	36.41	0.0301	30.60	0.0747
8	10	99	13.36	0.0638	14.37	0.0564	12.01	0.1068
9	0	8	1.32	0.2364	1.32	0.2364	1.32	0.2364

Taken as a whole these data meet the requirements of the hypothesis set. This, on the face of it, is rather surprising, for our test of the hypothesis depends on the proportion of diabetic siblings in the two crosses $Mm \times Mm$ and $Mm \times mm$, and our information about the presence of diabetics among these siblings depends upon the knowledge of the patient questioned. It seems not unreasonable to suppose that in a number of instances diabetic siblings exist who have not been recorded either because the patient (or any other relative questioned) simply did not know that his or her sibling had the disease, or because in certain instances diabetes may have been the cause of a death and not recognized as such. We have, in small measure, corrected for the latter possibility, for 6 of the siblings listed as diabetics in our tables presented symptoms of death so obviously the result of diabetes that they were at once so recorded, but it was impossible in many cases to obtain any reliable account of the ill and health of siblings.

Opposed to the probability that a number of diabetic siblings have escaped recording is the probability that a number of parents listed as heterozygotes (Mm) are really homozygotes (mm). The presence of genetically mm parents here classed as Mm would, of course, increase the expectation of mm offspring. The question then becomes: would the increased expectation of mm siblings due to the presence of unidentified but genetically mm parents seriously disturb our ratios, and to what extent would this increased expectation be balanced by the presumable presence of unidentified diabetics among siblings? A single illustration will suffice.

Let us suppose that in the 440 crosses listed as $Mm \times Mm$ 80 are really $Mm \times mm$, and that these matings produce the average number of diabetic children observed, *i. e.*, 3.398 *per* family or 272 children. Our calculated general expectation of diabetics in the $Mm \times Mm$ crosses is 4.35 per cent (*i. e.*, about 65 diabetics in 1495, see Table 4), so that presumably we would expect 11.83 diabetics in these 272 siblings. In the $Mm \times mm$ group our average expectation of diabetics is 11.04 per cent (*i. e.*, about 33 out of 299 siblings) so that we would expect 30.03 diabetics among the 272 siblings transferred now to the $Mm \times mm$ class. Our expectation of diabetics would then be increased by $30.03 - 11.84 = 18.20$ individuals; so that instead of expecting approximately 98 diabetics in the total population (Tables 4 and 5) we would expect $98 + 18 = 116$. The probable error for such an expectation would be approximately ± 6.64 individuals, so that the deficiency of 20 siblings engendered by the increased expectation would be barely significant. If this increased expectation were to be met exactly then we would expect that 20 of the 1698 siblings classed as non-diabetic were really diabetic but had been overlooked as a consequence of the defects of the method of obtaining family histories.

Now it happens that the median age of these parents is a little over 65 years. At this age a little over 50 per cent of the potential diabetics are identifiable as diabetics (see Table 3, columns 5, 8 and 11). Therefore our 80 diabetic parents may, on certain grounds, be taken as slightly more than $\frac{1}{2}$ the number of real diabetics, *i. e.*, mm individuals. Accordingly the illustration just given might very well apply except that a small proportion of the potential diabetics would be taken as mated to mm individuals already identified, *i. e.*, known diabetic parents, and the expectation of diabetes among the offspring would thereby be somewhat further increased.*

There can be, of course, no doubt that the proportions of diabetics in the two types of cross are significantly different. In the matings listed as $Mm \times Mm$ the observed percentage of diabetics is 4.28,

* To illustrate the complexity of the problem of deciding the proportion of the mm parents unidentified, the following two considerations may be mentioned. First, if, as seems not altogether unreasonable and is to some extent indicated in our data, there is a correlation between age of onset of diabetes in parents and in children, then, since we have chosen these families because at least 1 child is diabetic, the probability exists that an exceptionally large proportion of the parents capable of developing diabetes have developed the disease merely on the basis of the presumed parent-child correlation. Second, if we calculate the proportion of Mm to mm individuals in a Mendelian population breeding at random, then a general incidence of potential diabetics (*i. e.*, of mm individuals) of 4 per cent would require 88.9 Mm to 11.1 mm , or if the potential diabetics were equal to 3 per cent of the general population then the expected proportions would be 90.5 Mm to 9.5 mm . We actually have among these parents 91.9 non-diabetics to 8.1 diabetics. The maximum error in identification on this basis would be 27.03 per cent, indicating that at most some 22 mm parents are unidentified. This, of course, would make no significant alteration in the expected ratios among the children. But we are not at all certain that these parents are the result of random mating; nor are we certain of the general incidences of potential diabetics though crude estimates approximate those employed in this illustration.

and in the $Mm \times mm$ matings the observed percentage is 10.70. Since the median age of the siblings in the two groups is approximately the same, 42 years in the $Mm \times Mm$ group and 45 years in the $Mm \times mm$ group, the two crosses are crudely comparable on the basis of their percentage probable errors. The probable errors for the observed ratios among the siblings in the two crosses are respectively 0.35 per cent and 1.21 per cent, and the probable error of the difference is 1.25 per cent. The actual difference is 6.42 per cent which is 5.14 times the probable error of the difference, indicating a statistically significant difference between the 2 groups. Furthermore, if our classification of these matings is correct, and the age-distribution of the siblings roughly comparable, we should expect the percentage of diabetic siblings in the $Mm \times Mm$ group to be about $\frac{1}{2}$ the percentage of diabetic siblings in the $Mm \times mm$ group. If we calculate the expectation among the siblings on the basis of the average of 3.40 children *per* family in the $Mm \times Mm$ cross and 3.69 children *per* family in the cross $Mm \times mm$, the crude ratio of the expectations is 1:2.17. Or if we employ the approximate expectations of our tables (4.35 per cent to 11.04 per cent) the ratio is 1:2.54. The observed percentages, 4.28 per cent in $Mm \times Mm$ and 10.70 in $Mm \times mm$, are in ratio 1 to 2.50, and this is well within the margin of error. This may be taken to indicate that our classification of the crosses meets the Mendelian assumptions.

Further speculation is deemed fruitless, however, since the plain fact of the matter is that we do not know enough about the family history of the parents to enable us to calculate with any exactness the proportion of mm individuals among them. All that can be said is that on purely genetic grounds there is probably a greater deficiency of diabetic siblings than our tables (4 and 5) make apparent, but that this deficiency may be made up for by the fact that there exist a number of cases of diabetes among these siblings that our method of collecting the family histories failed to reveal.

The obvious moral to this situation is that the direct examination of every member of a diabetic family might very well obviate a number of pitfalls and uncertainties. This is, in fact, what we propose to do. In succeeding papers we shall present the statistics resulting from such examinations. It has been deemed advisable, however, to put on record the results of this inquiry into the family histories, and to reexamine these data and all that accrue subsequently, in the light of the results obtained from the direct examination.

That diabetes mellitus may be inherited has, of course, long been entertained as a possibility by numerous investigators (for references to the earlier literature see Baur, Fischer, and Lenz,³ Cammidge,⁶ Finke,⁷ Joslin,⁸ Kennedy,⁹ White,¹ and Wright¹⁰). The presentation of family statistics has generally been of two types: (1) The listing

of genealogies in diabetic families (see von Noorden,¹¹ Buchanan,¹² Hansen,¹³ Holst,¹⁴ Strange,¹⁵ Landsberg,¹⁶ Cammidge,⁶ Finke,⁷ J. S. Wright,¹⁰ *et al.*); (2) the listing of diabetes incidence among relatives of diabetics with little statistical analysis of the significance of these incidences (for examples, see Joslin,⁸ Finke,⁷ Høst,¹⁷ also John,^{18,19} Wendt and Peck²⁰). In none of the papers that have come to our notice have any direct attempts been made to ascertain the possible Mendelian basis of the disease. The statement has indeed been made by Buchanan¹² that diabetes incidences in 34 diabetic families examined by him do not support a Mendelian hypothesis, but he does not give details of his analysis, and the data of the genealogies that are figured in his paper as far as they go do support an hypothesis of recessiveness. The casual inspection of a genealogy, and the consequent observation of a deficiency of diabetics on ordinary Mendelian assumptions does not necessarily vitiate these assumptions, since a number of siblings or parents may either be too young to develop the disease or die before they have the chance to develop it. This has been very properly pointed out by Finke,⁷ and his data illustrate the point, though not *in extenso*. An ideal genealogy would be that of a family in which every member of the family had lived beyond the 9th decade, so that complete opportunity for expression of the disease were given to every member of the family. Even then one need not necessarily expect the calculated Mendelian ratios to obtain if the possibility exists that certain individuals who are potential diabetics never develop ascertainable symptoms of the disease. We have ignored this possibility in the treatment of our data, because it is unnecessary. What we have demonstrated is that the potentiality for developing diabetes behaves in these families *as if* it were a Mendelian recessive. We might conceivably be dealing with a dominant gene the expression of which is suppressed or not possible in a certain proportion of the cases, but this in no way detracts from the present analysis nor the practical consequences of it. Ideally we should have some specific test of latency that would obviate calculations based on age incidence.

Most investigators have been wary of accepting Mendelian interpretations, and very properly so. Their data are not of the sort that would enable a forthright decision. Any statistical analysis must depend on a knowledge of the ages of the non-diabetic as well as the diabetic members of the families examined, and if possible a knowledge of the family histories of the parents as well as the children. But it may be pointed out that if heredity is accepted as a factor in the etiology of the disease then this heredity must presumably be Mendelian. The known cases of non-Mendelian inheritance (*e. g.*, maternal inheritance of plastid characters in plants) are rare and rather special. The specific decision to be made is whether we are dealing with the expression of a dominant

or recessive gene or genes. Obviously one must choose the simplest explanation, and in the case of diabetes mellitus our data as far as they go support the notion of the inheritance of a single recessive gene.

Summary. The incidences of diabetes are significantly higher in families of diabetic patients than in families of non-diabetic patients. If we accept the assumption that potential diabetics before they develop the disease have the same expectations of life as persons generally, it can be demonstrated that the observed occurrence of diabetes in the children of the diabetic families is in accord with the hypothesis that potentiality for developing diabetes is inherited as a simple Mendelian recessive. The probability that certain parents classed as non-diabetic are genetically diabetic would indicate that there is, on our hypothesis, a deficiency of diabetic children in these diabetic families, but this presumed deficiency may be due to the limitations of the method of collecting family histories. In any event the data behave as if our identification of diabetics among the parents and children were in accord with Mendelian expectations, provided our calculations of the relative number of potential diabetics present in each decade are correct.

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THE METABOLISM OF LEVULOSE.*

I. SOME GENERAL CONSIDERATIONS ON PROVOCATIVE LEVULOSURIA.

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DURING the past 10 years the senior author and his associates have published a series of papers⁷⁷ embodying the results of extended investigations on the metabolism of galactose in man. Briefly summarized, these studies have shown that this sugar exhibits an interesting sex difference in the capacity for utilization which is tentatively ascribed, in part at least, to the specialized mammary mechanism of the female. Further, these studies have demonstrated that a wide variety of physiologic and pathologic conditions severally influence the tolerance levels in characteristic ways.

A survey of the fairly extensive literature on the metabolism of another hexose, levulose, discloses a series of seemingly significant differences in behavior from that shown by galactose in the same conditions. Obviously, these differences, if they could be confirmed, might throw more light on the complex interrelationships of our carbohydrate metabolism and equally could assume a differential meaning in some of the disease states with which they were associated.

Influenced by these considerations, studies have been undertaken, duplicating with levulose those already completed with galactose. The present paper is the first and preliminary report and embodies certain of the general considerations together with a few illustrative results from those already obtained.

Nearly 50 years ago, Hofmeister⁴⁷ studied the assimilation and utilization limits for a number of individual sugars, feeding them in graded dosage to fasting subjects and observing the level at which the sugar first appeared in the urine. This technique, with a variety of minor modifications, remained the basis of sugar tolerance testing until the development by Folin²⁴ and others of reasonably accurate microchemical methods for the quantitation of blood sugar turned attention to this method of approach. While the earlier

* Presented at the Forty-fourth Meeting of the American Physiological Society, Philadelphia, April, 1932.

blood sugar studies defined a series of curves which were regarded as characteristic of individual pathologic states,^{29,69} later investigations^{2,20,76,93} have cast grave doubt on the specific nature of these curves, have shown that other mechanisms are involved, and have sharply delimited the quantitative aspect of the method. In spite of these facts, blood sugar curves obtained by straight line interpolation between isolated points determined at conventional time intervals after a provocative test meal of glucose (100 gm. or 1.75 gm. per kilo of body weight⁵⁷), still remain the method of election of a large number of observers.

In 1899, Sachs⁸³ reported the interesting observation that dehepatized frogs showed a depressed tolerance for levulose but not for glucose or galactose. Two years later, Strauss⁹⁰ utilized this suggestion to develop a test for liver function with this sugar, and in subsequent papers^{91,92} reaffirmed its distinctive and differential character. In the supervening years a number of other investigators have applied the test, using either the urine or blood indications or both with reported results that are highly contradictory. While one group of observers^{8,13,19,26,30,40,85} for a variety of reasons find the levulose tolerance to be worthless as an index of disturbed liver function, Rebaudi⁷³ and many others^{18,27,32,55,81,82,91,92} report it to be a delicate indicator of certain types of hepatic derangement. Clinical reports of studies on groups of hepatopathies range from a 100 per cent positive response with 100 gm. of sugar^{18,81,82,91} to a 30 per cent indication under the same conditions.^{43,48} Several writers stress the point that the type of liver condition is an important factor in determining the response to levulose, since the relative amount of surviving functioning tissue may cause wide variation.⁵⁰ This serves both to explain certain of the discrepancies in recorded results and equally to offer information of possible differential value.

The recognition of departures from the normal presupposes the establishment of normal criteria; but here again wide fluctuations are reported, ranging from groups in which no case showed levulosuria after the ingestion of 100 gm. of sugar,^{82,91} to one series in which 57 per cent yielded positive urines after this test meal.⁶⁴ In another series 9 per cent were positive after 60 gm.,¹ while in yet another, 50 gm. gave an uniformly negative response.⁵⁵ Unfortunately, a large part of the measurements were made upon so-called "hospital normals," a fact which both invalidates the indications and offers a possible explanation for the discrepancies in the several reports. Goetsch, Cushing and Jacobson³¹ regard 100 gm. as the probable tolerance normal; v. Noorden⁶⁸ placed it as between 1.7 to 2.1 gm. per kilo of body weight.

On the basis of the urine findings, the tolerance is reported as depressed in syphilis,^{5,23} nephritis,^{17,27} tuberculosis,¹⁷ polycythemia,²⁸ and epilepsy;³³ and normal in leukemia,⁵ cancer,^{11,43,59} primary ane-

mia,⁵⁹ gastric ulcer,⁵⁵ and cystic ovaries,³² to name some among the many. There is a general downward tendency in pregnancy, although individual series show variations between 60 per cent³⁴ and 100 per cent.^{46,74} The worthlessness of the uncontrolled carbohydrate tolerance as a test for pregnancy has been too conclusively established to require comment here. Aberrations in the endocrinopathies are also reported (V.I.).

Whereas, a test meal of glucose—and in lesser degree galactose—will produce a significant rise in blood sugar, levulose exercises but slight influence on the observed levels in health. It is usually conceded to be abnormally high in liver cases,^{7,15,19,44,61,70,89,94,97} although occasional qualifying limitations are recorded.^{22,37,39,45} There is a definite lack of agreement, however, as to the line of demarcation between normal and abnormal increase, the range being from 4 mg. with 60 gm.⁶⁷ and 8 mg. with 45 gm.,⁶¹ through 20 mg.^{34,44} with 100 gm. to 30 mg. with 45^{19,94} and 36 mg. with a test meal of 100 gm.⁵³ The liver indices are usually given as more than 20 mg. with doses of from 30 to 50 gm.,³⁷ or that blood sugars following a test meal are indicative of hepatic dysfunction if they exceed from 125 mg.⁵⁸ to 135 mg.³⁷ Another criterion of liver involvement is a sharp rise and slow decline to the curve,⁴⁴ while a maximum at 34 to 37 minutes is regarded as normal.⁶⁶ Curves in pregnancy are recorded alike as normal¹⁶ and abnormal.^{46,60,67} Blood sugar levels indicate decreased tolerance in syphilis,³⁹ amebiasis,¹⁵ rheumatic heart,^{10,12} cancer of the pancreas,³⁷ chorea,¹² psychosis,⁸⁴ and malaria,⁹⁷ and are normal in ketosis,⁹ sprue,¹⁵ primary anemia,³⁸ pneumonia,⁹⁷ paralysis agitans,⁵² and following abortion.³⁵ Endocrine influences have also been studied.

These reports serve once more to emphasize the lack of value of the response of the "hospital normal" as the basis for the establishment of normal criteria. Further, it will be patent from the above brief review that the changes in blood sugar levels produced by test meals of levulose are even less well adapted than those obtained with glucose to indicate moderate divergences from normal function. Only incidental reference will be made to blood sugars in the remainder of this communication, as the topic will be treated in detail in a later paper. The present reports are based upon the urine findings following a modified Hofmeister⁴⁷ technique.

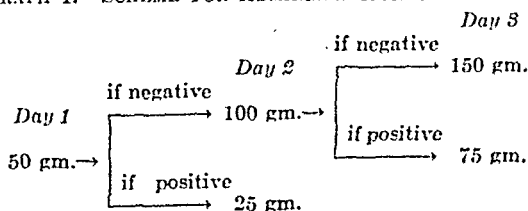
In determining tolerance limits, certain precautions must be taken if disturbing physiologic influences are to be excluded. Traugott⁹⁵ has emphasized the necessity of a preliminary diet control to insure normal tissue saturation, though Soisalo⁸⁸ feels this to be unnecessary, if blood sugar levels are the criterion. Fasting decreases tolerance,⁷⁵ exercise produces an opposite effect,^{4,49} unusual environmental temperatures may change the tolerance level.^{51,70}

The purity of the test sugar is of vital importance, particularly

if the urine findings are the indicator. Kraus and Ludwig,⁶² in 1891, found that 100 gm. of commercial glucose would produce melituria, while double that amount of a purified product yielded only negative results. Several later studies have substantiated this conclusion,^{23,96} and in the first paper Folin and Berglund²³ have emphasized the necessity of excluding from the test meal all reducing bodies which are capable of assimilation but not of utilization. The use of a sugar containing menstruum in which to administer the test meal,^{12,30,41,50} such as milk or natural fruit juices, should be wholly interdicted. Passing comment may be made on the proposal to use a mixture of sugars for the test meal;^{11,21,36,85} the procedure has nothing to recommend it and can readily lead to erroneous conclusions. With levulose, the need for purity becomes even more insistent, for reasons other than those already given. In most of the levulose now obtainable there is present an impurity which exercises a powerful laxative action on the gastrointestinal tract. Folin and Berglund²³ record disturbing experiences with levulose which had been autoclaved. We have had it uniformly with sugars from several sources which lacked final purification. Seemingly the substance can be eliminated by repeated recrystallizations from alcohol, but the product thus prepared is very expensive. Recent experience holds out the hope that a sugar can be prepared from the Jerusalem artichoke, at about one-fourth the cost of the other product, which is free from this disturbing substance. In the present studies only purified material has been used,* as diarrhea completely destroys the authority of the quantitative approach. It seems probable that some, at least, of the discrepancies in the previously reported assimilation limits of levulose may be ascribed to varying amounts of impurities in the several sugars used.

The general method of administering the graded doses of levulose followed that adopted originally for galactose, the higher tolerance of the former sugar determining larger individual doses. The plan can best be shown in the accompanying graph.

GRAPH I.—SCHEME FOR ADMINISTRATION OF LEVULOSE.



As the work has progressed, it has been possible to modify the program as presented to meet the needs of the individual case. As

* We are indebted to the Pfauastiehl Chemical Company (formerly the "Special Chemicals Company") of Waukegan, Ill., for a generous coöperation in the laborious purification of this material.

experience shows a definite upward or downward trend in a given condition, the initial dose may be selected accordingly and the test performed with a saving of time, money, and the patient's convenience. The technique of administration of the individual dose is given in Table 1:

TABLE 1.—DIRECTIONS FOR LEVULOSE TEST.

On the day of the test the following outline is to be observed:

1. At 5 A.M. void urine and discard.
2. At 7 A.M. void urine which has been gathering during the last 2 hours and save. This is Urine No. 1.
3. As soon as the urine has been voided, take the dose of sugar as sent, which you have dissolved in about 6 to 8 ounces of water ($\frac{1}{2}$ pint), drinking all of it. (Use more water with larger doses.)
4. At 9 A.M. collect the urine which has been gathering between 7 and 9. This is Urine No. 2.
5. At 11 A.M. collect the urine which has been gathering between 9 and 11. This is Urine No. 3.

IMPORTANT.

No food other than sugar is to be taken until 11 in the morning, at which time breakfast may be eaten. Water may be drunk reasonably. It is desirable that the patient remain in bed until breakfast.

Each urine should be placed in a separate container and carefully marked with the proper number. The name of the patient should be marked on the wrapped parcel. The entire collection should be sent to this laboratory as soon as completed, that is to say, in the afternoon of the day on which the test is made.

In the selection of cases for study, it was recognized that not only should the primary diagnosis be definitely established, but that complicating conditions, the presence of which could influence the tolerance level, must be equally carefully evaluated. To this end, each case studied was either given the full diagnostic procedure ("Long Form") described by one of us,⁷⁸ or its equivalent for those patients who could not be hospitalized for the entire period of study. The normal controls were given the morning study ("Short Form") described in the paper already cited,⁷⁸ such special tests as were indicated for the individual subject, and both the galactose and levulose tolerance determined as already described.

The urines were tested qualitatively with the well-known Benedict reagent⁶ and by the Seliwanoff⁸⁷ method. The quantitative measurements involved the Folin-Berglund procedure^{25,72} corrected for the levulose coefficient and the polariscope, clearing the urine with Lloyd's reagent, and applying the correction for the slight levo-rotation of normal urine as reported by Haas.⁴² Bulky urine samples were tested qualitatively and, if negative, concentrated and retested. This possibly disturbing factor can be readily controlled by reasonable regulation of the water intake during the test period. The full details of the analytical procedures for both urine and blood will be embodied in a subsequent paper. The methods used were selected after careful comparative study of existing procedures.

As stated earlier, the present paper is a preliminary communication and the data reported are illustrative of certain aspects of the study. The definition of normal standards of tolerance is the primary desideratum, as only by their establishment can departures be recognized and interpreted in terms of aberrant carbohydrate metabolism.

Control Group "A," the general data of which are given in the next table, was composed of 7 young women completing their third year of study in the Sargent School of Boston University who volunteered for this phase of the investigation.*

TABLE 2.—DESCRIPTIVE DATA.

Control Group "A" (Female).

Subject—	Ba.	De.	Fo.	Gr.	Ki.	Le.	Ro.
Age	20	20	21	20	20	20	22
Weight (deviation)	-5%	+1%	-2%	±0%	+3%	+40%	-7%
Lung volume deviation†	+6%	+13%	+2%	+7%	+16%	+8%	+4%
Urine	Nor.	Nor.	Nor.	Nor.	Nor.	Nor.	Nor.
Total nitrogen (gm.)	7.74	9.13	...	7.49	12.49	7.88	7.23
Blood chemistry	Nor.	Nor.	Nor.	Nor.	Nor.	Nor.	Nor.
Blood morphology	Nor.	Nor.	Nor.	Nor.	Nor.	Nor.	Nor.
Basal rate (deviation)	-10%	-6%	-6%	-11%	-6%	-2%	-5%
Blood pressure (mm.)	110/60	100/58	110/70	106/60	118/68	114/82	112/66
Pulse	72	62	70	60	68	64	72
Temperature (° F.)	98.2	98.2	98.2	98.0	98.2	98.6	98.2
Alveolar CO ₂ (mm.)	43	46	44	46	46	44	43
Galactose tolerance (gm.)	40	40	40	40	40	40	40

Carefully compiled medical histories gave no evidence of significant abnormality and the physical examinations were completely negative. We should like to stress at this point the necessity of such careful surveys to assure the normality of the "normal" control. All of these young women were in robust health and carrying successfully a full college program which, from the nature of the school, involved a daily quatum of active physical exercise. The one subject who was significantly overweight (Le) had a somewhat low sitting height index (0.516) which tends to exaggerate her departure from prediction. She was a large-framed powerful girl and the overweight seemingly no more than a personal characteristic. Two of the basal rates were low borderline values. This work was done in the spring, as the college year was approaching its end, and the senior author has frequently remarked a slight downward tendency to the respiratory metabolism of college groups at this season of the year. The results of the sugar tests with this group are collected in Table 3.

* The authors express their deep appreciation for this gracious cooperation.

† This term was adopted a number of years ago instead of the meaningless form "vital capacity." Perhaps "respiratory capacity" could still better be used to indicate this measurement, which is not to be regarded as vital.

TABLE 3.—SUGAR TOLERANCE.

Control Group "A" (Female). (All figures are in grams.)							
Subject:	Ba.	De.	Fo.	Gr.	Ki.	Le.	Ro.
<i>Galactose:</i>							
30 gm.	0	0	0	0	0	0	0
40 gm.	0.75	1.11	0.43	0.61	1.01	0.54	0.36
<i>Levulose:</i>							
75 gm.	0	0	0	0	0	0	0
100 gm.	0.16	0.11	0.16	0.13	0.12	0.14	0.13
125 gm.	0.20	0.31	0.22	..	0.19	..	0.23

All of the girls were positive with 40 gm. of galactose and negative with 30 gm., using the criterion as designated in the earlier galactose papers⁷⁷ of qualitative response to Benedict's reagent. With the levulose, both the Benedict test and that of Seliwanov were applied and where positive response was secured the amount of levulose was estimated quantitatively. All responded positively to the 100 gm. test meal, the amounts eliminated showing a surprising uniformity. The slight increase in the amount eliminated with the larger dose of 125 gm. is an interesting illustration of Allen's³ "carbohydrate paradox." The complete uniformity of the response of this group is fortuitous. The tolerance level indicated, however, is certainly not far from that which a larger series will define.

The volumes of the test urines varied from 65 to 195 cc. and showed no regularity in relation to the sugar content. Seemingly the water drunk during the collection period of 4 hours is the determining factor. Janney's⁵⁶ recent figures on forced water elimination are possibly significant in this connection. With the present group no effort was made to control water intake.

As Strauss' work on liver function may be said to be the starting point of provocative levulosuria studies, a few figures on the influence of hepatic dysfunction may next be considered. The significant data from a few cases are collected in the next table. It should be said in passing that the hepatic element in each case was established by careful clinical and laboratory studies, the details of which will be given elsewhere.

TABLE 4.—HEPATIC DYSFUNCTION, UNCOMPLICATED.

Sex.	No. of cases.	Galactose tolerance.		Levulose tolerance, average dose, gm.
		Response.	Deviation (%)	
Male	2	Normal	±0	63
Male	3	Depressed	-56	67
Female	9	Depressed	-61	53
Female	2	Depressed	-38	100
Female	4	Depressed	-50	156

The ages in this group ranged from 13 to 71 years with an average of 37 years. A partial review of the literature yields a group of 954 cases of liver dysfunction of highly diversified characters of whom 649 (68 per cent) gave a positive response to 100 gm. of

levulose. In one small group of 8 cases,⁵ 5 (63 per cent) were positive with 50 gm., while another author⁵⁵ reports 33 in 43 (77 per cent) positive with the same test meal. On the other hand, Friedman and Strouse³⁰ report a number of liver cases giving a negative response to 90 gm. of levulose administered in lemonade(!), and another investigation⁶³ reports a variety of hepatic conditions which responded uniformly in the negative to a test meal of 40 gm.

Our own figures show a considerable degree of variation, although 80 per cent give a positive response to 100 gm. or less. Interesting is the group of 4 women, all with depressed galactose tolerance, whose average response of 156 gm. suggests, at least, an increased tolerance. The senior author has already reported a like anomaly with galactose in liver cases.^{77h} The lack of quantitative correlation between the galactose and levulose results suggests once more the probability that the mechanism of utilization of the two sugars is probably not identical.

Lowered functional activity of the thyroid, where it affects sugar tolerance, determines an upward trend of modest proportions. In a long series of uncomplicated cases of hypothyroidism⁶⁵ the senior author, with galactose, has found two-thirds to be normal, the remainder demonstrating an average increase of some 30 per cent above prediction. In a paper recently presented,⁸⁰ one of us (A.W.R.) has pointed out the frequent association of hepatic dysfunction with lowered thyroid activity. In such cases, as might be anticipated, there is an usual depression of the carbohydrate metabolism, which is the expression of the algebraic summation of two opposite—and usually unequal—forces. In the next table are collected results from a small group of thyroid cases, a portion of which shows the liver complication.

TABLE 5.—THYROID FAILURE WITH (A) AND WITHOUT (B) HEPATIC COMPLICATION.

Group.	No. of cases.	Galactose tolerance.		Levulose tolerance, average dose, gm.
		Response.	Deviation (%).	
Thyroid alone:				
A	6	Normal	± 0	71
B	1	Increased	+25	Over 175
Thyroid-liver				
A	5	Depressed	-35	80
B	2	Depressed	-25	150

The galactose tolerances of the uncomplicated thyroid cases are in harmony with previous experience, the majority showing a normal value, and the exception an increase of modest proportions. The average for the levulose response of Group "A" is definitely below the 100 gm. level, which has been the criterion of many of the earlier observers while, equally, the single case with slightly increased galactose tolerance was negative with the somewhat massive dose of 175 gm. of levulose. Parallel records in the literature are few in number. In a paper previously cited,³⁰ the authors

administered 90 gm. of levulose dissolved in lemonade with the following results:

Three cases of hypothyroidism were negative, 9 in a group of 18 hyperthyroid cases were negative, and 5 cases of simple goiter were all negative. The authors note some uncertainty in the diagnoses as offered.

The group with hepatic complication parallels the record of the uncomplicated liver group, in quality at least. The figures are possibly suggestive; the limited number of cases argues for caution in interpretation.

The presence of an hepatic factor in many cases of toxic pregnancy renders data from this source apposite to the present discussion. A number of records from another investigation has been collected in the next table. Others, from a short series of normal pregnant women, are included as a rough control.

TABLE 6.—TOXIC AND NORMAL PREGNANCY.

Group.	No. of cases.	Months, average ante-partum.	Tolerance.	
			Galactose.	Levulose (av., gm.).
Toxic A	4	4 +	Depressed	44
B	13	2 +	Normal	56
C	3	1 +	Increased	75
Normal	9	3	Normal	72

At first sight there would seem to be some systematic relationship in the response to the two sugars, as with a rising galactose tolerance the relative capacity for assimilating levulose also increases. This seems to be a dependable datum. Although not all of these cases had a proven hepatic factor, the actual status of each case seemingly affects both sugars alike, at least in direction if not in amount. The same cannot be said for the apparent interdependence of the sugar on the time interval before delivery. The values are averages and the cases in the divergent groups are too few in number to give a final authority. That a trend is suggested may be conceded, however. The levulose figures for normal pregnancy are practically the same as for the toxic group with increased galactose tolerance.

In a series of 217 cases of presumed normal pregnancy drawn from a number of sources in the literature, 180 (83 per cent) were positive with the single test meal of 100 gm. of levulose. Van Creveld and Ladenius,¹⁶ in a series of 60 pregnant women, 53 of whom were in the first 3 months, found that 38 per cent were definitely positive and 9 more vaguely so with test meals of from 40 to 60 gm. of this sugar. On the other hand, Schroeder⁸⁶ found only 17 of 95 cases of pregnancy to be positive with 150 gm., and of this group only 3 gave a strong reaction in the urine.

The possible influence of pregnancy on the level of endocrine function of the ovaries⁷⁹ warrants survey of the results obtained

with groups in which ovarian function presents characteristic levels. These data are given in Table 7.

TABLE 7.—OVARIAN INFLUENCE.

Status.	Duration.	No. of cases.	Tolerance (average).	
			Galactose (gm.).	Levulose (gm.).
Normal, prepuberty	9	20	75
Normal, adult	15	40	108
Hypofunction	Years	4	20	75
Castration	Weeks	2	30	75
	"	1	20	75
	"	1	10	125
Castration	Years	3	20	125

Analysis of these figures presents some puzzling problems. The prepuberty child has a low galactose tolerance and responds uniformly to 75 gm. of levulose, while the tests with 50 gm. were equally negative. In adult years the galactose level doubles, but the levulose, while it follows the same directional trend, shows a very modest increase. Ovarian hypofunction produces a consistent lowering with both sugars, but in established castrates, though the galactose demonstrates the significant lowering to prepuberal levels elsewhere reported,^{77d} the levulose response is at a level superior to the average value for the intact adult. Three of the 4 early castrates show a levulose response consistent with that of galactose. The fourth, on the other hand, shows too low a galactose and too high a levulose to be harmonious with the other data. A possible injury to the central nervous system, disclosed by the complete study of the patient, would account for the abnormal galactose level, but raises a new question in regard to the levulose metabolism. But little added information may be derived from the literature. Coppioli¹⁴ reports a lowered tolerance in aged women and there are a few animal experiments which equate but ill with studies in man.

While, as stated initially, the results here presented are in the nature of illustrations to some of the general considerations, the implications of the data presented may be briefly discussed.

Discussion. It would seem probable that there is a fairly well defined zone for normal individuals within the limits of which doses of levulose will commonly produce transitory levulosuria when the sugar is administered with due regard to certain standardizing conventions. Among these should be named a preliminary establishment of reasonable tissue saturation, the administration of a very pure sugar without admixture of uncertain amounts of foreign sugars, the application of the test to subjects in an initial basal condition, and the avoidance of exercise and exposure to extremes of temperature during the test. Levulose shows a definitely higher level of utilization than does galactose, the ratio being apparently of the order of about $3 \pm$ to 1. In general, conditions producing fluctuations in the galactose tolerance engender like changes in

that of levulose which are usually similar in direction but not in amount. Hepatic dysfunction of various types affects the utilization of both sugars. The anomalous increase in tolerance already observed with galactose seemingly finds more frequent expression when levulose is ingested. The influences of some of the function levels of individual endocrine glands on galactose utilization are not always directly reflected with that of levulose. Jacobson⁵⁴ had already noted differences in the behavior of glucose and levulose in hypophysectomized dogs with Eck fistulæ.

In other words, preliminary study of the levulose tolerance in a series of small groups of selected cases demonstrates these differences from the behavior of galactose in the same conditions that were broadly suggested by a review of the literature. The verification and definition of these and other differences and similarities will be treated in later papers.

Summary. A brief review of some of the existing literature on levulose tolerance has been made and the numerous contradictions found therein noted.

A standard technique based on the Hofmeister procedure for the determination of the tolerance has been outlined. The necessity for the use of very pure sugar and certain other limiting conditions have been emphasized.

A series of comparative studies on selected groups has been carried out with both galactose and levulose. Observed coincidences and discrepancies are recorded and lead to the conclusion that there are real differences in the mechanism of utilization of the two sugars.

NOTE.—The authors wish to express their indebtedness to the members of the Evans staff who coöperated in the diagnostic procedures and to the subjects of these investigations who cheerfully made the sacrifices necessary for the performance of these studies.

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THE INCIDENCE AND SEVERITY OF ARTERIOSCLEROSIS IN THE ORGANS FROM FIVE HUNDRED AUTOPSIES.*

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A COMMON diagnosis made in the clinic and at the autopsy table is that of "generalized arteriosclerosis." Often it is the only diagnosis; more frequently it is used to explain such complexes as "essential hypertension," or "cardio-renal vascular disease." The clinician discovers that his patient has hypertension, finds the peripheral arteries hard, tortuous and supposedly sclerotic, elicits, perhaps, signs of myocardial degeneration or of disturbed kidney function, and consciously or unconsciously he thinks of them in terms of a widespread arteriosclerotic process. The pathologist, on the other hand, may encounter difficulties when he attempts to correlate the clinical with the pathologic findings. Often the most careful examination fails to show a generalized sclerosis of the vascular system in the literal sense of the term. The vessels of some organs are

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affected to a marked degree, those of others not at all or only slightly, and frequently the vascular tree of a particular organ is not uniformly involved.

With these and related facts in mind the present study of 500 autopsied cases was undertaken to determine the incidence, distribution and degree of arteriosclerosis in the various organs of the body.

Review of Literature. As the literature on the distribution of arteriosclerosis is meager and widely scattered, a short résumé may be of value. Dow,¹ using as criteria the degree of hardness and thickness of the arterial walls of 8 cadavers in the dissecting room, found that the abdominal aorta, femoral and popliteal arteries were most frequently and most extensively affected, whereas the mesenteric arteries were strikingly seldom the seat of degeneration. In the pelvis the internal iliacs and the parietal vessels were more often involved than the external iliacs or the visceral vessels. The arteries of the lower extremities were more commonly sclerotic than those of the upper. The arteries which supply the cerebrum were of especial interest: that portion of the internal carotid artery which lay in the cavernous sinus, particularly the bifurcation into the anterior and middle cerebral arteries, frequently presented sclerosis of a very advanced degree. This was in marked contrast to the cervical portion of the internal carotid, which seldom showed degeneration. The tricuspid valve and the pulmonary artery were not implicated in any case, but the mitral valve and the thoracic aorta were often the sites of sclerotic processes.

Brooks² studied the incidence of visceral arteriosclerosis as revealed by gross examination, utilizing only those cases in which arterial changes were of a sufficiently pronounced character to influence obviously the clinical as well as the anatomic manifestations. His results represent, therefore, large vessel sclerosis. The order of frequency of involvement in 368 cases was as follows: aorta (333 cases), coronary vessels (270), brain vessels (132), renal vessels (81, all with marked involvement), pancreas (74), hepatic vessels (43), splenic vessels (35), lungs (11), coeliac axis and its visceral branches (19) with a diffuse involvement of the mesenteric vessels in 4 cases, and the spinal vessels in 20.

Norris and Landis,³ quoting Rokitsky, state that the frequency with which the different parts of the arterial tree are most affected is: aorta (arch, descending and abdominal portions), iliacs, crurals, coronary arteries and cerebral arteries. They emphasize that arteriosclerosis may be selective and unequally distributed throughout the body: "The pipestem radials of the day laborer are often associated with fairly good visceral arteries and in such cases constitute a benign form not at all incompatible with long life."³

The incidence of sclerosis in the arterioles and small arteries has been investigated by a number of workers. Jores⁴ found changes most frequently in the arterioles of the kidney, spleen and pia mater;

less frequently in those of the stomach, intestines and liver. The coronary vessels were unique in that the arterioles were always free from involvement even when the larger branches were markedly diseased. Fahr⁵ and Herxheimer⁶ confirmed the findings of Jores. Fahr reported that of 44 cases of hypertension the small arteries of the pancreas were involved in 38 of them. He especially noted that the gastro-intestinal tract was rarely implicated. Herxheimer stated that arteriosclerosis of the spleen occurred with increasing frequency from early youth to old age and was present in a majority of elderly patients, apparently without relation to hypertension.

Studying arteriosclerosis in relation to renal disease, Evans⁷ found that a diffuse hypoplastic sclerosis was most common in the kidney. It was not found in other organs unless also present in the kidney and spleen, where the lesions were always more marked. In its typical development this form of arteriosclerosis is not encountered in the heart, lung or skeletal muscle.

Evans⁸ also studied the incidence of arteriosclerosis in 4 children. He writes, "The incidence of the lesion (arteriosclerosis) in the various organs follows that found in adults in its main features, that is to say, the kidney and spleen are most affected, the pancreas and suprarenals are next in order, the affection of the intimate vasculature of the liver is slight and the heart escapes. It is noted that the vessels in the brain were not affected in these cases, whereas those in the stomach were." In these two respects the incidence of the lesion is different from that in adults.

Fishberg⁹ states that in 72 cases of essential hypertension which came to necropsy, lesions of the terminal arterioles were invariably present. In all his cases the arterioles of the kidney were involved. The splenic arterioles were affected in two-thirds of the cases, the pancreatic in one-half and the cerebral in one-fifth, but the lesions even when present in these organs were not as marked as those in the kidney. The myocardium, lungs, gastro-intestinal tract and thyroid were rarely implicated and then only to a minor degree. The author stresses the point that the distribution of arteriolarsclerosis differs from that of "large vessel atherosclerosis." The latter has its site of predilection in the heart, brain and extremities, while arteriolarsclerosis is most frequent in the kidney, spleen and pancreas. Bell and Clawson,¹⁰ although they did not analyze their hypertensive cases statistically, nevertheless were of the opinion that Fishberg's results expressed the true distribution of visceral arteriosclerosis.

The incidence of arteriolarsclerosis in cases of hypertension was found by Bordley and Baker¹¹ in 23 cases to be as follows: Kidney 95.8 per cent, adrenals 79.2, pancreas 70.7, brain 58.3, heart 50.0, liver 25.0, and lung 16.0. Unfortunately no data for the spleen are given, but otherwise the results agree with those of the foregoing authors. Branch and Linder¹² found arteriolarsclerosis most frequently in the kidney, spleen and pancreas in the order given.

Klemperer and Otani¹³ in a study of malignant nephrosclerosis reported visceral arteriolar sclerosis in every case. The pancreas, liver and adrenal were involved in about the same percentage as in simple hypertension. In addition they found arteriolar sclerosis in all the kidneys examined. The spleen was excepted on the basis of the extreme frequency with which arteriolar hyalinization was found in this organ.

Arteriolar sclerosis of the vessels supplying the voluntary muscles is thought by most workers to occur rarely. Watanabi,¹⁴ in an extensive investigation of 116 cases of so-called generalized arteriosclerosis, found only 6 with involvement of the small arteries of the skin. Even when the lesion was widespread in many organs, Jores⁴ and Fahr⁵ were unable to demonstrate arteriolar sclerosis in skeletal muscle or skin. Branch and Linder¹² reported a similar condition in the arterioles of voluntary muscle. During the examination of 6 cases of nephrosclerosis, Klemperer and Otani¹³ found no evidences of sclerotic lesions in the arterioles in either the abdominal muscles or the diaphragm. Evans⁷ reports that diffuse hypoplastic sclerosis is not found in its typical development in the skeletal musculature. The terminal arterioles of the skin and voluntary muscles were found by Fishberg⁹ to be rarely involved, and then only to an insignificant extent.

On the other hand, Kernohan and his colleagues¹⁵ observed from biopsies on the voluntary muscles of ambulatory patients with diffuse, hypertensive, vascular disease, that the arteries often showed distinctive histologic changes. In those who later came to autopsy, lesions were found identical with the arteriolar lesion previously described at biopsy, as well as arteriosclerotic changes in many other organs. Kernohan's viewpoint is supported by the work of Sutton and Brandes,¹⁶ who found that of 3040 autopsies performed at the Cook County Hospital 340 (11.1 per cent) showed gross arteriosclerosis and of this number 113 (32.2 per cent) had peripheral arteriosclerosis. Unfortunately the value of their work is diminished by the fact that the authors did not define their use of the term "peripheral arteriosclerosis." Recently Horine, Weiss and Beard¹⁷ have reported a series of 11 patients who had "hypertensive heart disease without hypertension" (*sic*). Biopsies taken from the deltoid muscle revealed alterations in the intima and media of the arterioles similar to the changes described by Kernohan and his collaborators. The 1 case which came to necropsy disclosed a generalized arteriolar sclerosis.

Materials and Methods. The protocols and microscopic sections of 500 autopsies performed at the University and Philadelphia General Hospitals during 1925 were reviewed. While these autopsies were not consecutive, they were nevertheless unselected and hence may be regarded as representative of the pathologic services of two large hospitals. They possess the common feature that in all

cases sections were taken from both domes of the diaphragm. One has, therefore, in every case, the vessels of this skeletal muscle to compare with those of the various other organs. The postmortem records were searched for mention of gross arteriosclerosis, the following arteries being considered: The coronaries and the large arteries of the kidney and brain. In the microscopic sections the vessels examined were the small, unnamed branches of the visceral arteries and the arterioles. The degree of sclerosis was designated as being "mild" or "marked." In grading the sections two factors were kept in mind. First, the degree of involvement of the individual arteries and, second, the proportion of the total number of arteries affected in the particular sections studied, these being regarded as representative of the whole organ. The vascular changes classified as "mild" arteriosclerosis consisted of fatty changes in the intima varying from inconspicuous lesions to definite microscopic atheroma, and of a distinct thickening of the intima produced by the formation of new connective tissue. As "marked" arteriosclerosis were classified changes of a more advanced degree, such as greater thickening of the intima, hyalinization, fragmentation or reduplication of the internal elastica and involvement of the media.

TABLE 1.—THE INCIDENCE OF ARTERIOSCLEROSIS FROM GROSS EXAMINATION OF HEART, KIDNEY AND BRAIN.

Organ.	Number of cases.	Normal vessels (per cent).	Mild sclerosis (per cent).	Marked sclerosis (per cent).	Total sclerosis (per cent).
Heart . . .	405	42.5	23.4	34.1	57.5
Kidney . . .	442	44.2	20.0	36.0	56.0
Brain . . .	90	20.0	17.8	62.3	80.1

TABLE 2.—THE INCIDENCE OF ARTERIOSCLEROSIS FROM MICROSCOPIC EXAMINATION.

Organ.	Number of cases.	Normal vessels (per cent).	Mild sclerosis (per cent).	Marked sclerosis (per cent).	Total sclerosis (per cent).
Heart . . .	346	45.7	26.5	22.7	49.2
Lung . . .	426	66.1	25.1	8.5	33.6
Spleen . . .	426	10.9	24.4	64.9	89.3
Kidney . . .	470	26.5	26.3	47.1	73.4
Liver . . .	448	71.7	18.9	9.5	28.4
Pancreas . .	148	42.6	35.1	22.3	57.4
Brain . . .	89	18.0	19.2	63.0	82.2
G. I. tract .	70	57.9	27.9	14.3	42.2
Adrenal . . .	75	38.7	29.4	32.0	61.4
Diaphragm .	498	94.5	5.6	0.0	5.6

Results. The cases have been grouped into two tables (results of gross and microscopic examination) without reference to age, sex or race. In Table 1, the results of gross examination of the arteries of the organs at the autopsy table, only four organs are represented as the data concerning the others were insufficient. It indicates that the heart, kidney and brain were often implicated by an arteriosclerotic process of a degree sufficiently advanced to be recog-

nized grossly. In Table 2, the results of a microscopic examination of the arteries of the various organs, it is seen that the diaphragm, liver, lungs and gastro-intestinal tract had normal arteries in more than 50 per cent of the cases. Indeed, evidences of sclerosis were found in the diaphragmatic vessels in only 5.6 per cent of the 498 cases examined, and even this small percentage displayed but a mild involvement. The spleen, brain, kidney and adrenals exhibited, in the order named, the greatest incidence and the most marked degree of sclerosis.

A very interesting feature appears in Table 3, where the organs were arranged in the order of decreasing incidence of arteriosclerosis. It was found that those organs which were most often involved were also most markedly affected by an arteriosclerotic process. The arteries of the spleen, brain and kidney were sclerotic, for example, in 70 per cent or more of the cases and of these at least 60 per cent were involved to a marked degree. In the diaphragm, liver, lungs and other organs which are infrequently implicated, one noticed a high incidence of the milder forms of sclerosis and a low incidence of the more advanced forms. The diaphragm illustrated this point very well: of a total percentage of arteriosclerosis of 5.6, no case showed marked involvement. In the liver and lungs less than one-third of the sclerotic cases were involved to a marked degree; whereas 60 to 75 per cent of the same cases exhibited milder forms of the lesion. The heart, pancreas and adrenal showed an approximately equal incidence of mild and of marked arteriosclerosis. An important exception is the interesting fact that the brain, although it did not show the greatest total percentage of arteriosclerotic cases, did present the highest incidence of marked involvement.

TABLE 3.—ORGAN INCIDENCE OF MARKED VERSUS MILD ARTERIOSCLEROSIS.

Organ.	Total per cent of sclerosis.	Per cent of total sclerosis with marked sclerosis.	Per cent of total with mild sclerosis.
Spleen	89.3	72.6	27.4
Brain	82.2	76.8	23.2
Kidney	73.4	64.5	35.5
Adrenal	61.4	54.3	45.7
Pancreas	57.4	38.9	61.1
Heart	52.9	45.0	55.0
G. I. tract	42.2	33.3	66.7
Lung	33.6	25.0	75.0
Liver	28.4	33.6	66.4
Diaphragm	5.6	0.0	100.0

Among the 500 autopsies studied there were 303 males and 197 females. The youngest case was a 6 months' fetus, born prematurely, and the oldest was a man aged 92 years. In order to condense the data, the cases were divided into three age groups, 0 to 29 years, 30 to 59 years and 60 to 92 years, which correspond approximately

to youth, middle and old age. Table 4 records the incidence of arteriosclerosis in both sexes for each of the age groups. It is difficult to correlate the occurrence of sclerosis in males and females because of an insufficient number of cases in the same groups, but on the whole it was approximately equal in the two sexes. The table indicates that the incidence and degree of arteriosclerosis increased with the age factor. It need occupy us only long enough to draw attention to three organs: the spleen, kidney and diaphragm. In the spleen and kidney the high incidence of arteriosclerosis became gradually more evident as the age factor advanced, until finally, in the group comprising those cases between 60 and 92 years, more than two-thirds of the cases showed marked sclerosis. In the diaphragm, however, the great majority of the arteries were free from sclerosis even in the advanced age group.

TABLE 4.—PERCENTAGE INCIDENCE OF ORGAN ARTERIOLARSCLEROSIS IN BOTH SEXES IN YOUTH, MIDDLE AND OLD AGE.

Degree of sclerosis.	Sex.	Heart.	Lung.	Spleen.	Kidney.	Liver.	Pancreas.	Brain.	G. I. tract.	Adrenal.	Diaphragm.
<i>0 to 29 years (77 cases).</i>											
Normal vessels	M	86.3	93.6	34.4	82.8	91.4	81.8	100.0	85.8	50.0	97.4
	F	89.0	89.4	27.8	85.0	94.0	86.6	75.0	83.4	87.5	100.0
Mild sclerosis	M	10.3	6.4	51.7	17.2	8.8	18.2	0.0	14.3	50.0	2.6
	F	11.1	8.6	55.6	10.0	6.1	13.4	25.0	0.0	0.0	0.0
Marked sclerosis	M	3.4	0.0	13.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	F	0.0	2.9	16.7	5.0	0.0	0.0	0.0	16.8	12.5	0.0
<i>30 to 59 years (235 cases).</i>											
Normal vessels	M	54.4	71.5	9.0	31.4	71.9	43.6	29.1	55.0	50.0	96.9
	F	32.8	67.3	8.0	47.1	65.4	33.3	18.7	64.3	38.5	96.4
Mild sclerosis	M	31.4	22.4	28.6	38.9	19.2	36.4	25.8	30.0	26.9	3.1
	F	47.2	26.9	27.3	25.9	19.4	25.0	37.4	14.3	30.8	3.6
Marked sclerosis	M	18.2	6.0	62.5	20.5	8.9	20.0	45.2	15.0	23.1	0.0
	F	20.0	6.0	65.0	26.9	15.3	41.7	43.8	21.4	30.8	0.0
<i>60 to 92 years (182 cases).</i>											
Normal vessels	M	16.0	41.6	5.4	8.5	62.6	20.0	0.0	42.8	5.6	91.6
	F	13.2	60.3	1.5	1.4	66.6	22.7	7.7	38.4	44.5	85.0
Mild sclerosis	M	25.2	41.6	9.8	16.0	24.0	34.3	9.1	21.4	38.9	8.3
	F	25.0	22.2	6.0	21.9	24.3	45.4	7.7	30.8	22.2	15.1
Marked sclerosis	M	58.8	16.9	84.9	75.5	13.6	45.7	91.0	35.7	55.6	0.0
	F	61.8	17.5	92.4	76.6	9.1	31.8	84.5	30.8	33.3	0.0

Discussion. With the exception of the results presented in Table 1 the study deals almost entirely with the arterioles and minute arteries of the organs.

Perhaps the most striking feature of the investigation was the rarity of sclerosis of the diaphragmatic arteries. This organ, one of continuous activity, has a very rich blood supply, yet seldom were its arteries found to be sclerosed and then but mildly. The relative infrequency of sclerosis in the arteries of the muscles is substantiated by the results of all workers with the exception of Kernohan and his collaborators, to which it is in marked contrast.

The spleen is of equal interest. All investigators seem agreed that it is more frequently the seat of arteriosclerosis than any other organ, with the possible exception of the kidney. More remarkable still, the spleen is usually affected to an advanced degree. Why this organ should be so peculiarly singled out for a degeneration of its arterial walls remains a mystery.

The investigations reported here and in the literature indicate that a truly generalized arteriosclerotic process of a degree sufficiently advanced to be of clinical importance occurs infrequently. It is true that marked sclerosis of the arteries of the spleen, kidney and brain is often found at autopsy and is in all probability a common occurrence during life; however, it is equally evident that other organs such as the lungs, liver, gastro-intestinal tract and particularly the voluntary muscles are seldom severely implicated.

The practical significance of the results is clear: a diagnosis of generalized arteriosclerosis should be made with caution and only on the basis of adequate evidence. The clinical features in such cases should be carefully correlated with the histologic findings at autopsy, for it is only in such a manner that clarity on this subject will be reached.

Summary. 1. An analysis of the incidence and severity of arteriosclerosis in the organs from 500 unselected autopsies is presented.

2. The order of frequency with which the arterioles and small arteries of the organs were affected was: spleen, brain; kidney, adrenal, pancreas, heart, gastro-intestinal tract, lungs, liver and diaphragm. This is in agreement with the observations of most investigators.

3. The arteries of the organs which were most frequently involved were also most markedly affected; conversely those that were least often involved showed mild degrees of arteriosclerosis.

4. The vessels of the diaphragm were infrequently implicated.

5. The incidence and degree of arteriosclerosis increased with the age factor.

6. The reports from the literature and the results of this study indicate that a generalized arteriosclerotic process of a degree sufficiently advanced to be of clinical importance occurs infrequently.

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ALLERGY IN HYPERTENSION.

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IN 1930 Waldbott¹ reported some cases of essential hypertension who were members of allergic families, in whom there were sensitivities to foods or other allergens. The blood pressure in these individuals was lowered when the allergens to which they were sensitive were avoided, and returned to a high level on contact with them. He concluded that "some cases of unexplained hypertension may be caused by allergy."

This is a very attractive hypothesis because, if proved to be true, it will offer an effective method of treating hypertension.

Since one of us (M.H.F.) had available a large number of patients with hypertension who had been studied for a long period of time, and in whom the variations in pressure from month to month on various types of treatment were known, we decided to investigate this subject. It seemed to us desirable to begin with patients with hypertension who also had allergic manifestations, and to use cases without these symptoms only if favorable results were obtained.

Among several hundred patients with hypertension in the clinic

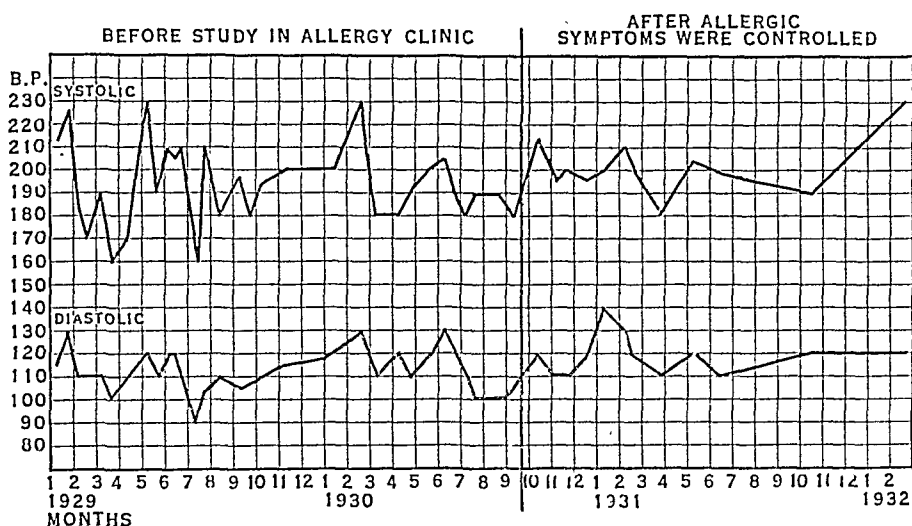
of Mt. Sinai Hospital only a few were found who had allergic symptoms. Since hypertension has an incidence increasing with age and allergy one decreasing with age, this dearth of material presenting both conditions is not surprising.

The following 2 cases from the clinic and 1 from private practice were selected:

Case Reports. CASE 1.—C. M., a white woman, aged 50 years, first came to our attention, June 8, 1929, complaining of substernal pressure, breathlessness on slight exertion, palpitation and cough. The symptoms were of about 3 years' duration, but had been growing progressively worse. The past history was essentially negative. Physical examination showed an obese female moderately dyspneic and orthopneic. The lungs were emphysematous. The apex beat of the heart was palpable in the 5th interspace at the anterior axillary line. There was a systolic murmur audible at the apex and the base. The second aortic sound was accentuated. The heart rate was 120 per minute, rhythmic and regular. The blood pressure was 226 systolic and 110 diastolic. The arteries showed moderate peripheral sclerosis. The edge of the liver was difficult to palpate, but there was tenderness below the right costal margin. There were varicose veins in both legs and slight pretibial edema. The blood Wassermann test was negative. The Roentgen ray showed moderate diffuse dilatation of the aorta, left ventricular hypertrophy and pulmonary congestion. The eye grounds showed tortuous vessels and the picture of retinal arteriosclerosis. The electrocardiogram was negative except for an inverted *T* wave in Lead III. The urine showed a small amount of albumin and a moderate number of leukocytes. The blood count and the blood chemical studies showed normal findings. In August, 1930, the patient was referred to the allergy department because of recurrent attacks of hives. She was found to be sensitive to cottonseed and was desensitized during September and October, 1931, and cottonseed products were removed from her diet. She has had no further allergic skin manifestations. Although she stated that she feels better since being treated in the allergy department there has been no lowering of the blood pressure level. Her blood pressure, taken on August 16, 1932, was 220 systolic and 130 diastolic.

CASE 2.—A. R., a colored female, aged 54 years, was first seen on March 30, 1928, complaining of pain in the eyeballs, occipital headaches, dizzy spells, palpitation on slight exertion, occasional slight swelling of the ankles and a general feeling of weakness. She had been told that she had had high blood pressure 6 years before, and had had a slight stroke 3 years before, which left her with a barely perceptible weakness of the left arm and leg. The past history was otherwise negative. Physical examination showed a well-developed and well-nourished colored female, not dyspneic nor orthopneic. The lungs were negative. The apex beat of the heart was just beyond the left midclavicular line in the 5th interspace. There was a faint systolic murmur at the apex and the second aortic sound was accentuated. The heart rate was 58 per minute, rhythmic and regular. The blood pressure was 220 systolic and 120 diastolic, and there was slight peripheral sclerosis. The liver was not enlarged and there was no edema. The orthodiagram showed considerable enlargement of the heart to the left with moderate dilatation and increased density of the aorta. The electrocardiogram was normal except for left axis deviation. The blood Wassermann test was negative. The urine showed a specific gravity varying between 1012 and 1023, albumin varying from 0 to +, and microscopically a few leukocytes. The patient was followed in our hypertension clinic from April, 1928, to September, 1929, when she was referred to the allergy department.

During this period she had had several transitory attacks of urticaria associated with some edema of the angioneurotic type. In the allergy department she was found to be sensitive to meats (beef, pork and mutton) and molluscs (clam, oyster, crab, lobster, scallop, shrimp) and told to abstain from the above-mentioned products. She has had no further attacks of urticaria or angioneurotic edema, but her blood pressure has not fallen to any degree (Chart I).



is shown by Chart II, taken from a previous study² in which it was demonstrated that the sodium chlorid content of the diet did not affect the blood pressure level. Symptomatic improvement in hypertension follows many types of treatment, but the blood pressure changes are within control limits despite the symptomatic improvement.

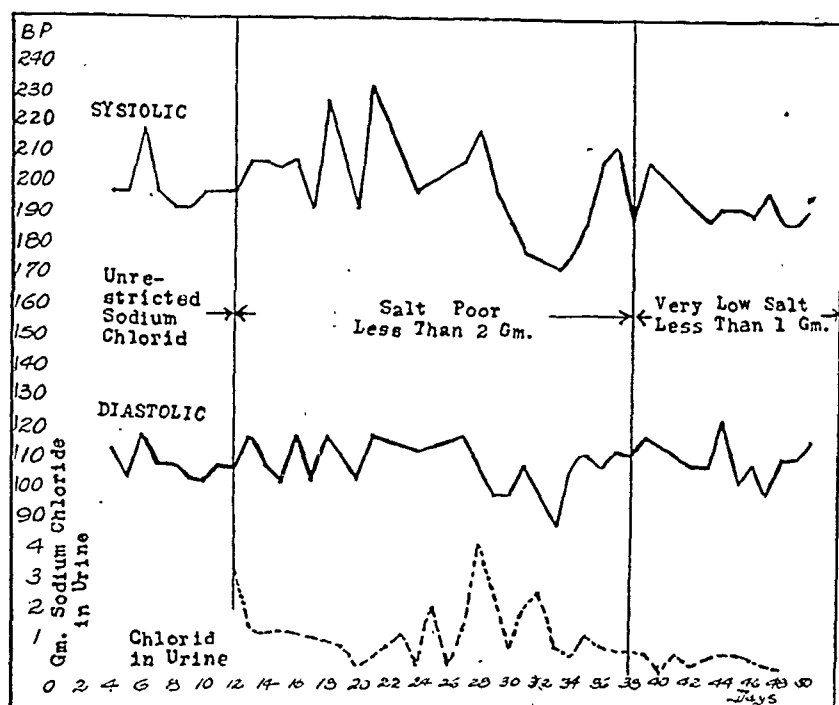


CHART II.

Summary and Conclusions. Three cases of hypertension without kidney failure, having allergic symptoms in addition to their hypertension, were studied by allergic methods.

The allergic symptoms were controlled in all of them. All patients felt better but the hypertension persisted. No relationship between the blood pressure level and the allergens could be demonstrated. Furthermore, hypertension and allergy are found infrequently associated in the same patient.

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UNUSUAL CHANGES IN THE ELECTROCARDIOGRAMS OF PATIENTS WITH RECENT CORONARY OCCLUSION.*

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HERRICK,¹ Smith,^{2,3,4} and Pardee^{5,6} first demonstrated definite changes in the form of the electrocardiogram in recent coronary occlusions. Following their work many further case reports have appeared, so that certain features of the electrocardiographic picture have now been fairly well established. The earliest change is a noticeable deviation of the *S-T* segment from the isoelectric level. Later the *S-T* segment becomes isoelectric, shows an upward convexity and is followed by a negative pointed *T* wave with rounded shoulders. In successive records the *T* wave waxes and wanes in amplitude until only an inverted *T* wave remains. This large, negative *T* wave is the coronary *T* wave of Pardee⁶ and the "cove-plane *T*" of Rothschild, Mann and Oppenheimer.⁷ Parkinson and Bedford⁸ have divided the electrocardiographic changes into two types, *viz.*, the *T*₁ type with the *S-T* segment elevated and the *T* wave negative in Lead I, and the *T*₃ type in which these changes in the *S-T* segment and *T* wave occur in Lead III. However, the literature also contains many cases of recent coronary occlusions diagnosed clinically or proven postmortem, in which the electrocardiographic findings do not fit into the characteristic pattern.

It is now also well recognized that the rapidity and extent of the change in the electrocardiogram in successive records is more striking in recent coronary occlusion than in probably any other type of lesion. It is therefore the common practice to take a series of curves in cases of suspected recent coronary occlusion. In reviewing many of the published series, transitions are seen which, if judged by a single curve, without the series, would not be considered typical. Some of these earlier changes are so significant that we believe they may often furnish a clue to the presence of a coronary occlusion before more typical electrocardiographic changes occur. In fact, they may be present in cases of coronary occlusion which never develop the characteristic electrocardiographic form. In this study we attempted to identify some of the changes in a series of electro-

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cardiograms which we believe to be significant of coronary involvement but which are not accepted generally as diagnostic, and to illustrate and compare some of the less commonly seen changes in the more typical forms.

All of the patients here reported—except Case 11—had attacks clinically diagnosed as recent coronary occlusions and their histories are typical of the commonly accepted criteria for this diagnosis (see case reports). Case 11 is a “rheumatic heart” case presented to contrast the electrocardiographic appearance with that of Cases 9 and 10.

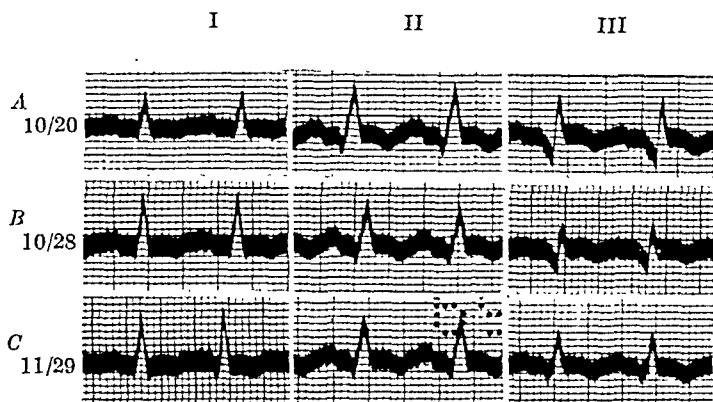


FIG. 1.—(Case 1.) *A*, 1 day after an attack; *B*, 8 days later after another severe attack on the same day. Patient died on December 31, 1931, and autopsy showed a thrombosis of the descending branch of the left coronary artery.

Atypical S-T Segment and T Wave Changes. Case 1 (Fig. 1) shows negative *T* wave in all 3 leads. Similar cases have been reported by Parkinson and Bedford,⁸ Smith,⁴ Willius and Barnes,⁹ and Willius.¹⁰ There is “low voltage” in this case, and a definite *Q* wave is present in Leads II and III to which Pardee,¹¹ Parkinson and Bedford⁸ and Wilson *et al.*¹² ascribe some significance. The electrocardiographic findings in this case are suspicious although not typical of recent coronary occlusion. This patient died on December 1, 1931, and at autopsy a recent thrombosis of the descending branch of the left coronary artery was found.

Transient elevation of the *T* wave is shown in Cases 2 (Fig. 2), 3 (Fig. 3), and 4 (Fig. 4). Such slight, rapid changes are, we believe, to be regarded as suspicious of a recent coronary occlusion. In none of these cases did the electrocardiograms obtained ever assume the form regarded as characteristic, although the clinical picture in each case was that of coronary occlusion (see case reports).

Case 2 (Fig. 2) died on February 23, 1932, and at autopsy advanced coronary sclerosis and myocardial fibrosis were present. In view of the autopsy his attack may be regarded as an angina pectoris, and this patient resembles the case reported by Katz and

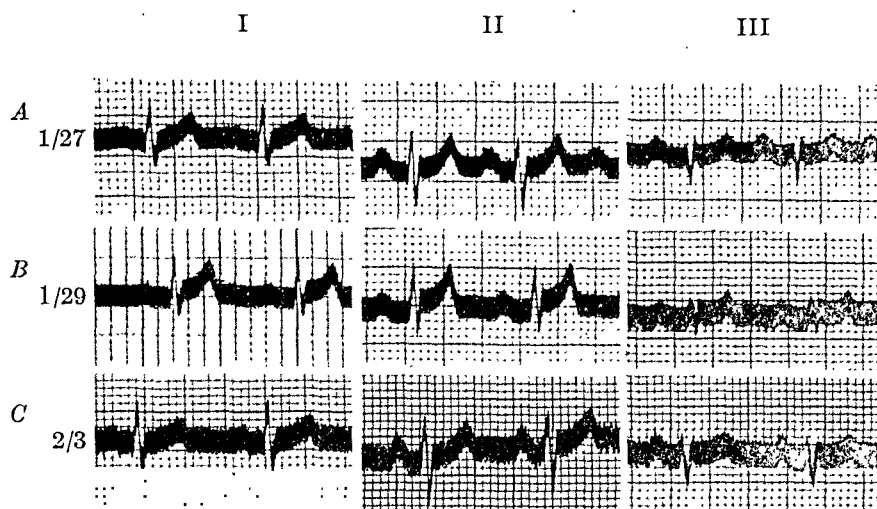


FIG. 2.—(Case 2.) *A*, 2 days before attack of pain; *B*, 6 hours after the attack. Patient died on February 23, 1932. Autopsy showed coronary sclerosis and myocardial fibrosis, but no occlusion of coronary arteries.

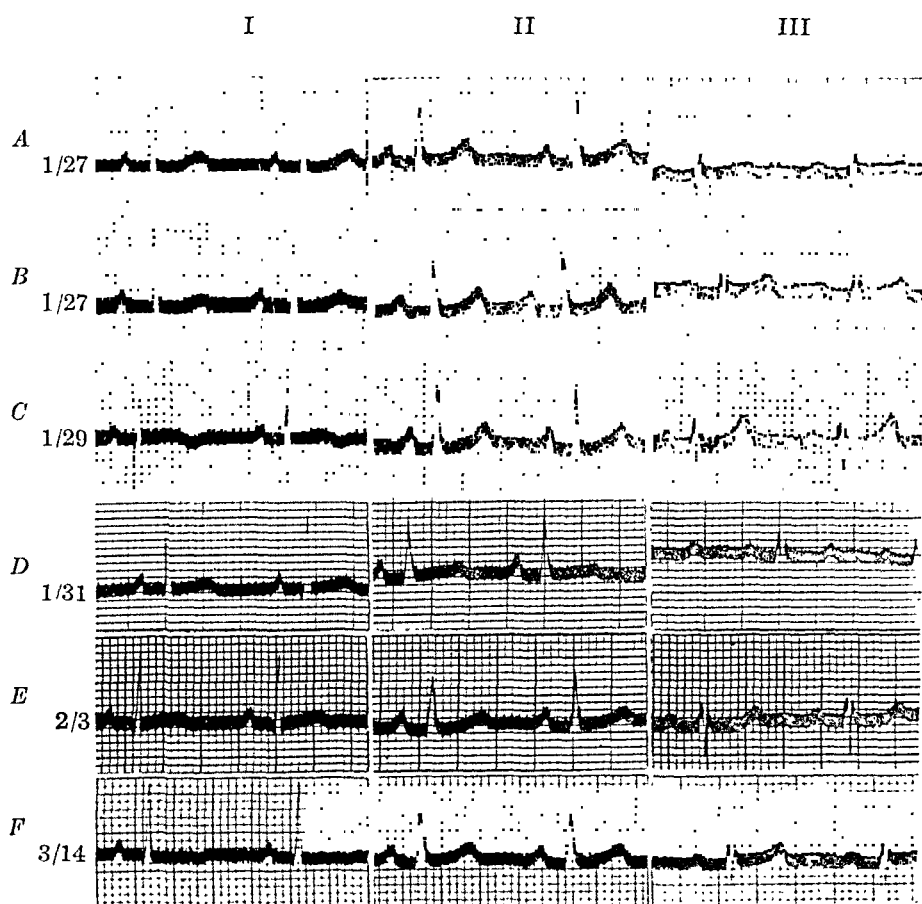


FIG. 3.—(Case 3.) *A*, a few hours after the attack; *B*, 7 hours later on the same day.

Wallace.¹³ The changes in the electrocardiogram 6 hours after the attack are unusual in that the elevation of the *S-T* segment and the *T* wave (Fig. 2, Segment *B*) are just the reverse of the changes described by Feil and Siegel,¹⁴ and Parkinson and Bedford¹⁵ during attacks of angina pectoris.

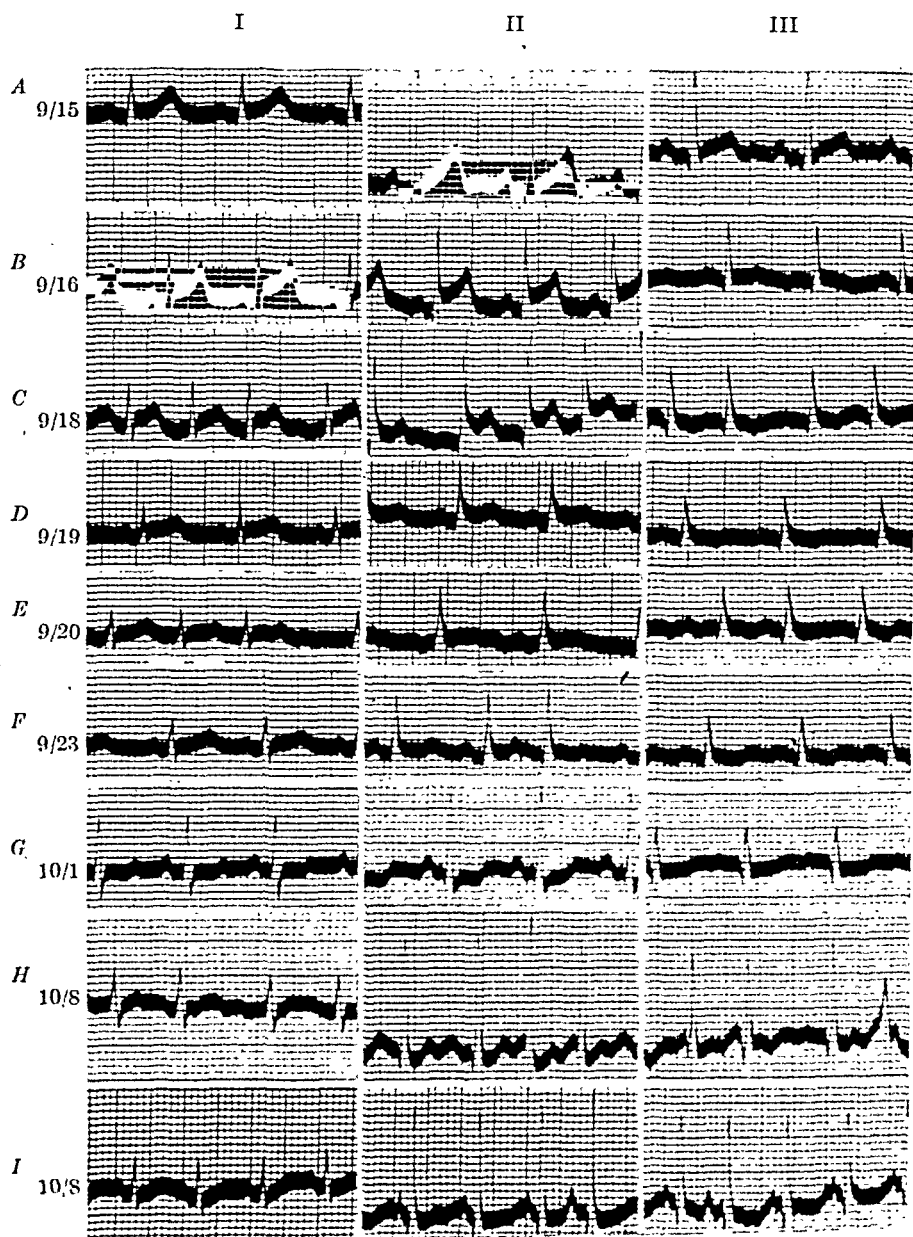


FIG. 4.—(Case 4.) *A*, a few hours after the attack; *G*, pneumonia developed.

Case 3 progressed until a definite inversion of the T wave appeared in Lead I and the elevation of the T wave increased in Lead III (Fig. 3, Segment C). In the course of the next few days further slight changes in the form of the T waves occurred.

Case 4 (Fig. 4) shows transient T wave changes which in Segments B and C are accompanied by a definite elevation of the S - T segments. Auricular fibrillation was present at times (Fig. 4, Segments C, E, and H). Following the development of pneumonia on October 1, 1932, a negative S - T segment appeared in all leads (Segment G) which decreased before death. The cause of this reversal may be due to a generalized ischemia of the heart following pneumonia. Such a generalized ischemia has been shown experimentally by Feil, Katz, Moore and Scott¹⁶ to lead to such depressed S - T levels in the dog.

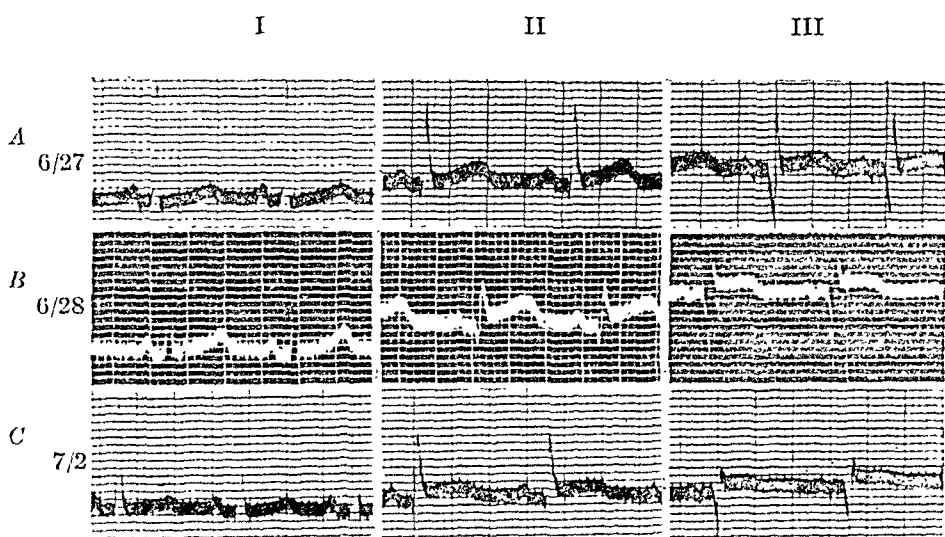


FIG. 5.—(Case 5.) A, 5 days after attack.

The most striking feature of Case 5 was the S - T elevation (Fig. 5). The first two curves were taken a few days after the attack and show a definite elevation of the S - T segment in Leads II and III. Four days later (Fig. 5, Segment C) the S - T levels in Leads II and III became somewhat lower and the T wave smaller in all leads. Unfortunately, no further records were taken, so it is impossible to know whether or not the characteristic coronary type of curve developed subsequently. However, the S - T elevation and the slight T wave changes, together with the Q wave in Leads II and III seem sufficient electrocardiographic evidence of a coronary occlusion in such a case.

A depression of the S - T segment in all 3 leads is the striking feature in Case 6 (Fig. 6). The T wave is upright in Lead I and it is difficult to identify the T wave in Leads II and III. There is a

peculiar notching of the *S-T* segment and the difference in the duration of the *S-T* segment in the separate leads is unusual. The notch on the *S-T* segment was located in the same spot of the cycle in the auricular extrasystoles (last beat L. II, Segment *B*, Fig. 6) as in the sinus beats, ruling out the possibility that these notches were *P*

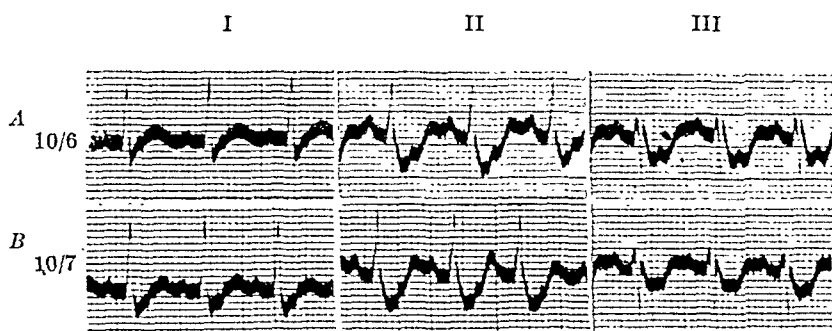


FIG. 6.—(Case 6.) *A*, 4 days after attack.

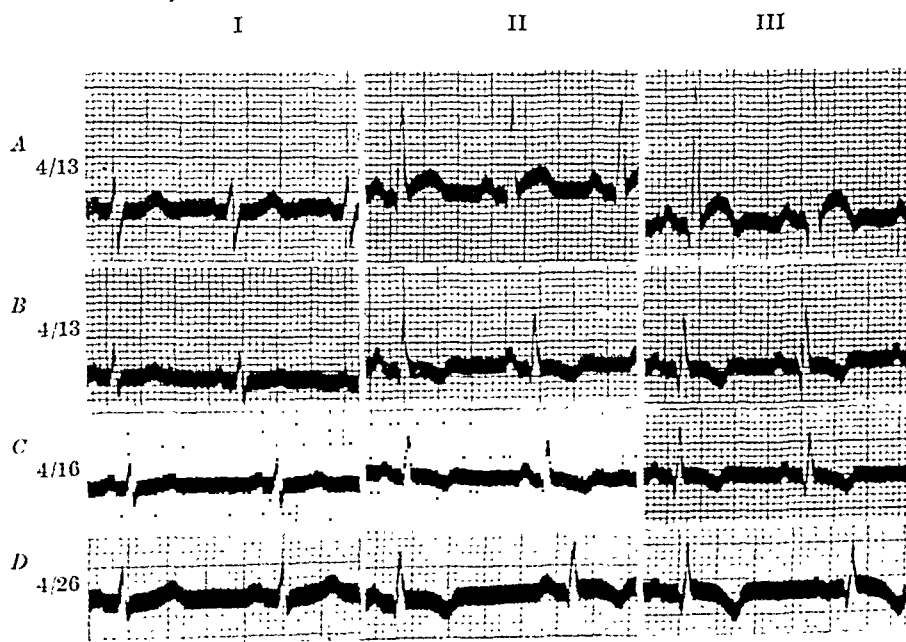


FIG. 7.—(Case 7.) *A*, the day of attack; *B*, several hours later on the same day.

waves and the mechanism auricular flutter. This case is presented to show that sharply depressed *S-T* segments may be present without the so-called high "take-off" and, while rare, are probably just as diagnostic of recent coronary occlusion as a high elevation of this interval.

The records of Cases 1, 2, 5 and 6 and some of the records of Cases 3 and 4 do not fit into the T_1 or T_3 types of Parkinson and Bedford classification.

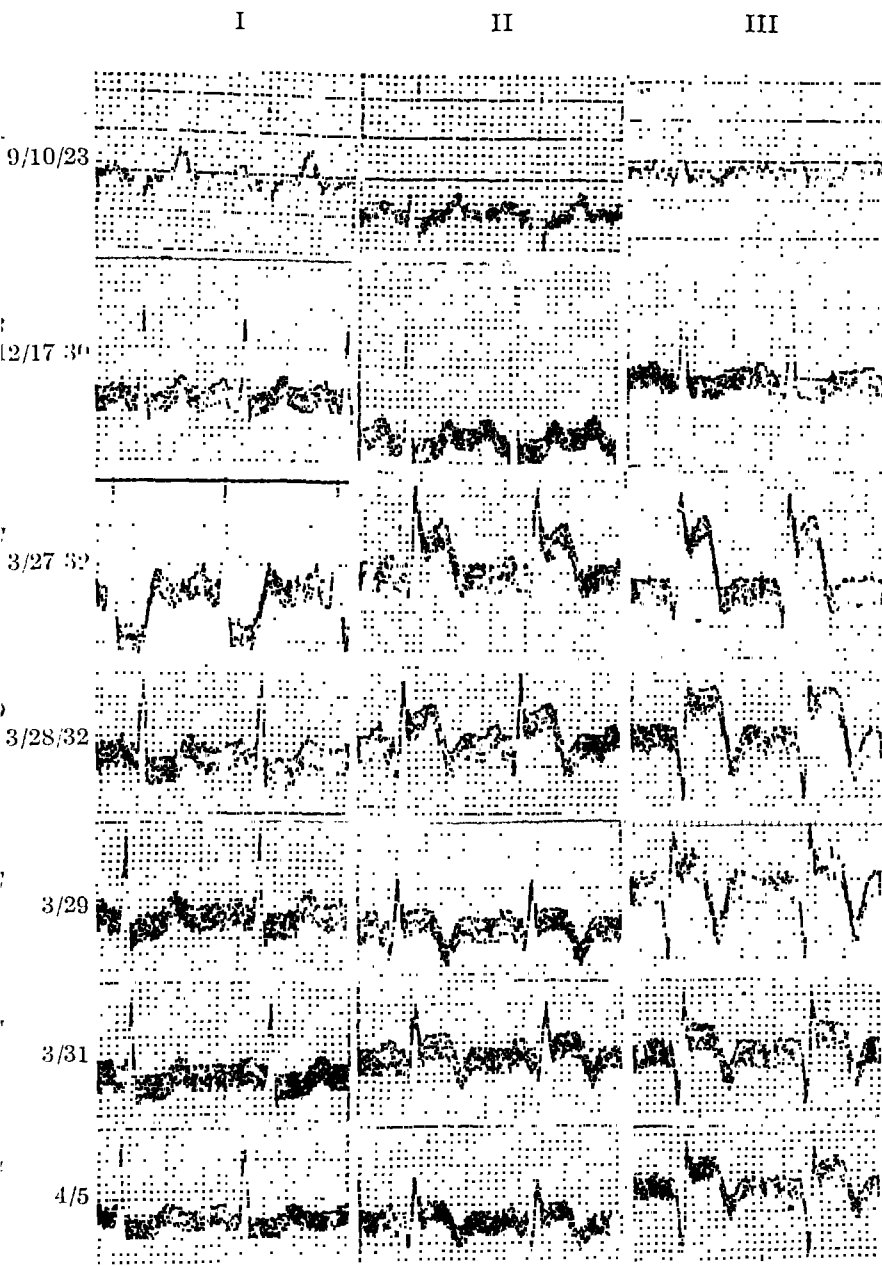


Fig. 8.—(Case 8.) A, 9 years before a severe attack; B, 2 years before attack. Patient has precordial pain; C, a few hours after attack.

Rare Forms of the T_3 Type. The T_3 type is well illustrated in Cases 7 and 8 (Figs. 7 and 8). The first record of Fig. 7 (Segment A) was taken very soon after the attack which occurred in the hospital. There is a definite elevation of the S-T segment in Leads II and III with the typical "hump," and a Q wave is also present in Lead III.

Another curve taken a few hours later (Fig. 7, Segment *B*) shows the typical cove-shaped inversion of the *T* wave in Leads II and III, and the *S-T* segment has returned to the isoelectric level. Very little further change occurred in the next 13 days. The first two curves illustrate the rapidity with which changes may take place.

In Case 8 there is an even more striking illustration of the T_3 type with a perfect example of the monophasic stage (Fig. 8, Segment *C*). The first tracing (Fig. 8, Segment *A*) was taken in 1923, shortly after the first symptoms of discomfort were observed, and showed nothing definitely abnormal. The second (Fig. 8, Segment *B*) taken in 1930 showed a negative *S-T* segment in all leads and a small negative *T* wave in Lead III, which was suggestive of some myocardial involvement. A few hours after a severe attack on March 27, 1932, another tracing was taken (Fig. 8, Segment *C*). This is a typical monophasic curve, with the entire ventricular complex greatly depressed in Lead I except for an early spike (*Q-R-S* complex) and a late wave (*T*), and markedly elevated in Leads II and III with only an early spike (*Q*). On the following day (Fig. 8, Segment *D*) the *S-T* segment in Lead I became less depressed, the *T* wave remaining upright. The *T* waves in Leads II and III became definitely negative and cove-shaped although the "hump" of the *S-T* segment remained. The *S-T* segments and *T* waves in subsequent records gradually changed in a typical manner, but the curves in the 2 months following were still decidedly abnormal and the *S-T* segments in Leads II and III had not reached the isoelectric level.

Probably the majority of cases go through the monophasic transitory stage within a few hours or possibly even minutes after an attack, and since in many instances records are not obtained until a day or so after the attack the monophasic stage is comparatively rarely obtained. It is unusual for the transition to be as slow as in Case 8. Pardee,⁶ Scott,¹⁷ Katz and Wallace,¹³ and Moore and Campbell¹⁸ have reported similar monophasic curves.

*Unusual T_1 Type, with the Upright *T* Wave Unusually Tall in Leads II and III.* Cases 9 (Fig. 9) and 10 (Fig. 10) resemble the T_1 type described by Parkinson and Bedford⁸ in that the *T* wave is inverted and cove-shaped in Lead I and upright in Lead III. However, the outstanding feature of these curves is the tall, upright, peaked *T* waves in Leads II and III (Fig. 9, Segments *A*, *B* and *C*, and Fig. 10, Segments *D* and *E*). These *T* waves in Leads II and III, if seen in a mirror in an inverted view—in other words, in inverse image—exactly resemble the inverted cove-shaped *T* wave characteristic of coronary occlusion. Fig. 11 shows the 3 leads of Case 9 printed in inverse fashion and except for the inverted "*P*" and "*Q-R-S*" waves, this record looks like a classical T_3 type of curve taken some time after a coronary attack (*viz.*, the curves of Fig. 8).

Case 10 (Fig. 10) shows the transition of the *T* wave in Lead I from

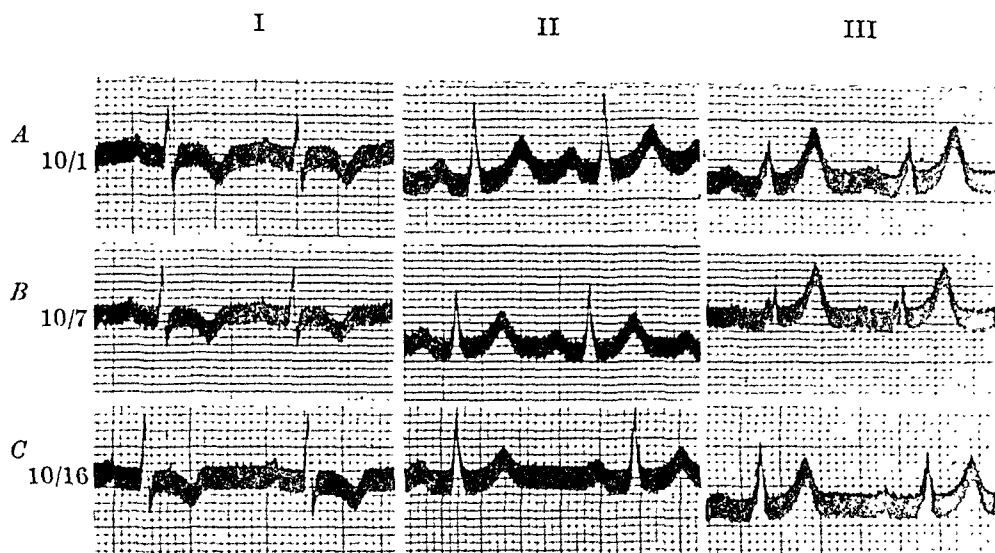


FIG. 9.—(Case 9.) A, 1 month following attack.

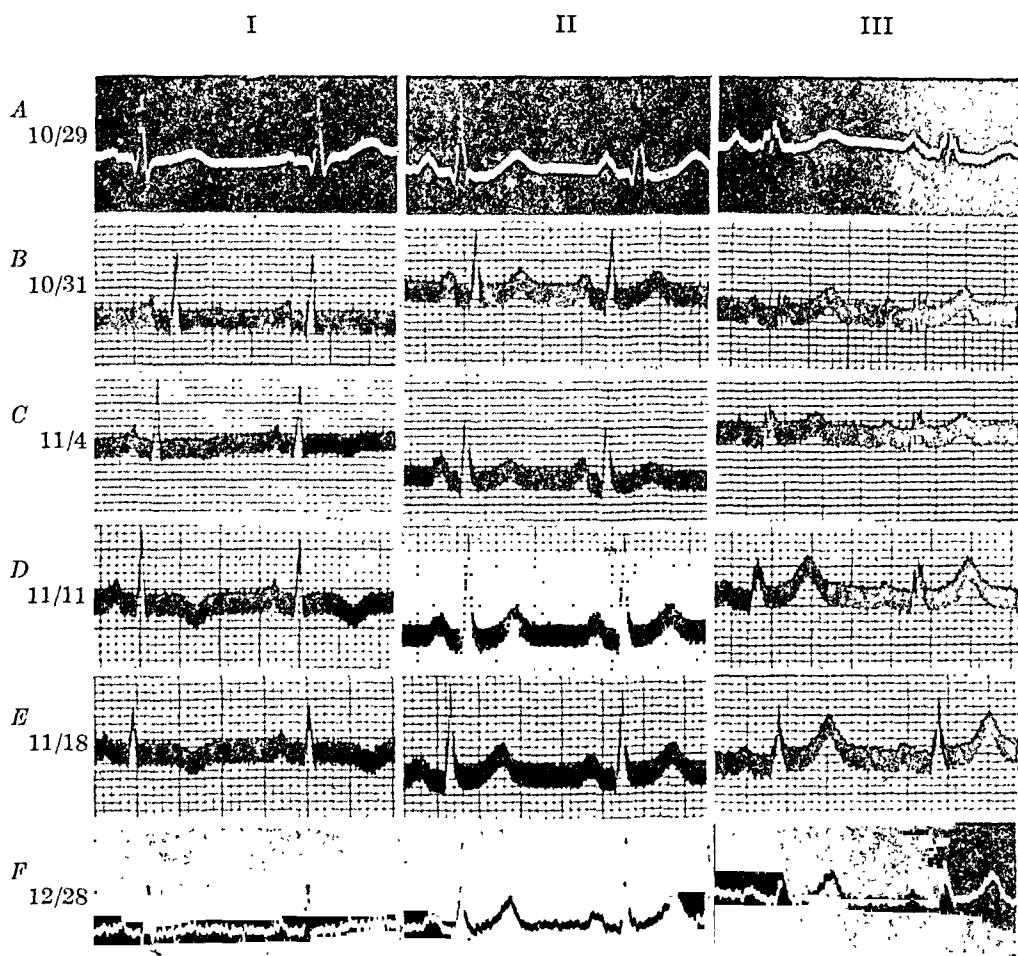


FIG. 10.—(Case 10.) A, the day of attack.

an upright to an inverted one and in Leads II and III from a small to a tall, peaked *T* wave which later decreased in size (Fig. 10, Segment *F*).

So much attention has been paid to the large negative *T* wave in coronary occlusion that sight has been lost of the fact that the inverse image of this in an upright large *T* wave is just as characteristic. In published series illustrating electrocardiographic changes in coronary cases this change in an upright *T* wave to a taller and more peaked one is often present, although seldom pointed out as being especially significant in itself. Levine's series¹⁹ shows several such curves, *viz.*, Fig. 16, 19, 39 and 49; Parkinson and Bedford⁸ (*viz.*, Cases 7, 8 and 10) and Moore and Campbell¹⁸ also have published such records, and Wilson *et al.*¹² have described such curves. But none of these authors has pointed out that the upright *T* wave is so similar in shape and contour to the inverse image of the characteristic inverted cove-shaped coronary *T* wave. In view of these reported cases changes in an upright *T* wave, such as we have shown in Cases 9 and 10, are just as significant of a recent

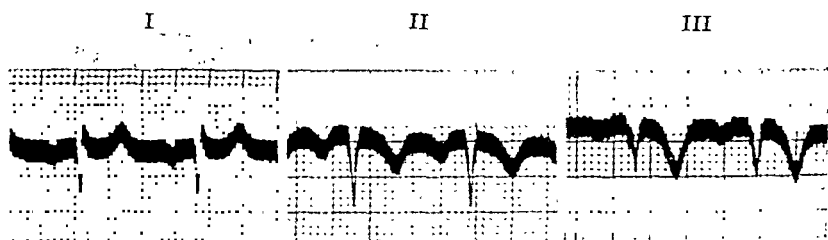


FIG. 11.—Segment A of Fig. 9, printed in inverse form.

coronary occlusion as their inverse image, the inverted, cove-shaped *T* wave. Furthermore, the inverted, cove-shaped *T* wave may be absent or, if present, may be much smaller and less noticeable than the upright *T* wave here shown.

Elevation of the *T* wave is known to occur in a number of conditions such as rheumatic heart disease, thyroid disease, pneumonia, and others, but the contour of the *T* wave and the *S-T* segment in such cases is different from the elevation here described. Fig. 12 is an example of the elevated *T* wave not specific for recent coronary occlusion. The second curve (Fig. 12, Segment *B*) taken in 1931, about 1 year after the first tracing and at the time a murmur was first detected, shows an elevation of the *T* wave in all 3 leads. The *T* wave in Lead II is especially tall. The contour of the *T* wave is quite different from that seen in recent coronary occlusion in that it has no rounded shoulders, its two limbs are not symmetrical, the descent being much steeper than the ascent, and the transition of its descent with the horizontal is more abrupt than that of its rise. The *S-T* segment also lacks the "hump." The contrast

between the upright *T* waves in non-specific and in coronary occlusion can best be seen by comparing this curve with Figs. 9 and 10.

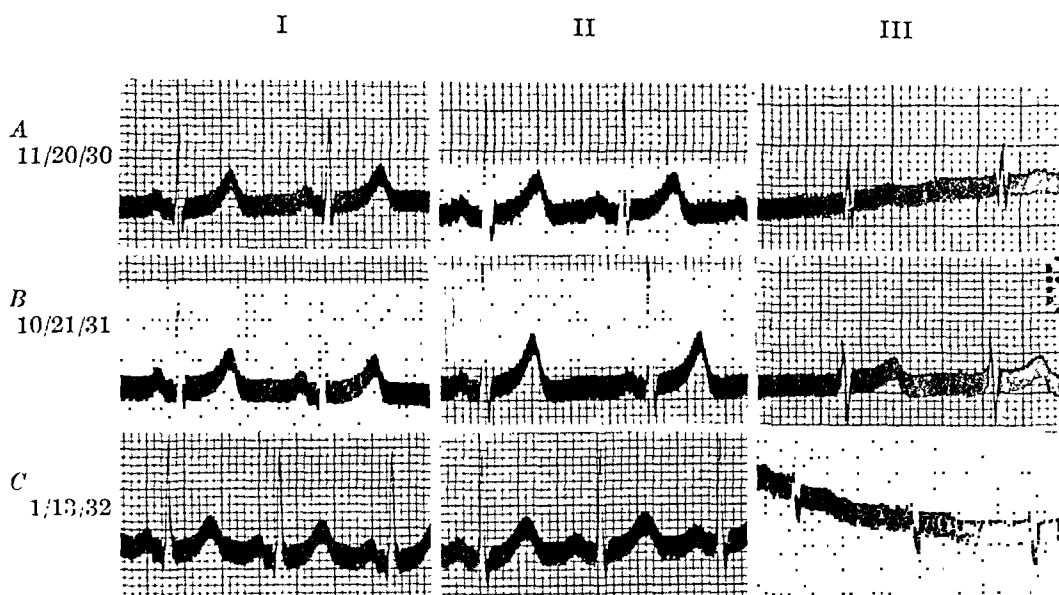


FIG. 12.—(Case 11.) A case of rheumatic heart disease.

Case Reports. CASE 1.—S. N., male, aged 59 years, 2 years before entrance into the hospital had his first coronary attack; 18 months later he had another, after which he was in bed much of the time. The day before entering (November 19, 1931, on Dr. Sidney Strauss' service) he had a typical severe attack which left him prostrated. While in the hospital he grew steadily worse, having frequent attacks of pain and dyspnea. He died on December 31. At autopsy a thrombosis of the descending branch of the left coronary artery was found.

CASE 2.—S. G., male, aged 67 years, was sent into the hospital in January, 1932, by Dr. B. Rappaport, with definite signs of hyperthyroidism; the basal metabolic rate was +42.7. While preparations were made for operation he had a sudden attack which was diagnosed clinically as a coronary occlusion. He had typical pain, a fall in blood pressure, elevation of temperature, rapid pulse, etc. Later he developed a bronchopneumonia, and died 3 weeks later (February 23). At autopsy advanced coronary sclerosis and myocardial fibrosis were present. Many atheromatous plaques were found in the coronary arteries which narrowed the lumen but did not completely occlude any vessel.

CASE 3.—M. E., male, aged 63 years, had no symptoms until 10 days before his attack, when he became short of breath on slight exertion. He was sent into the hospital by Dr. J. Meyer on January 27, 1930, with a characteristic attack of coronary occlusion with pain, leukocytosis of 18,400, and a drop in blood pressure. When he left the hospital he was entirely free of pain and discomfort.

CASE 4.—A. S., male, aged 47 years, entered the hospital on Dr. Schiller's service, September, 1930, because of an infected hand, and had no history of previous angina pectoris. While in the hospital he was suddenly seized with a very severe substernal pain which radiated toward the neck. Respiration became rapid and labored. His face was ashen; the lips had a cyanotic

tinge. His temperature was 101° F. and the blood pressure dropped to 70 mm. Hg systolic and 50 mm. Hg diastolic. The leukocyte count was 12,600. A diagnosis of a recent coronary occlusion was made. The patient continued to be very ill and auricular fibrillation developed. Roentgen rays showed a diffuse bronchopneumonia. The patient became worse and died, but no autopsy was obtained.

CASE 5.—M., female, aged, 63 years, 2 months before coming to the hospital had attacks of substernal pain radiating to both arms. At the time she was sent in by Dr. W. Buchbinder (June 27, 1930) she had clinical symptoms of recent coronary occlusion such as pain, dyspnea, cyanosis and a leukocytosis of 15,000. Somewhat later a precordial friction rub was heard and she had a temperature of 103° F. She had severe attacks of paroxysmal dyspnea and the blood pressure dropped considerably. After a month in the hospital she was much improved and went home.

CASE 6.—N. H., female, aged 63 years, was sent to the hospital by Dr. F. Beaumont on October 6, 1930, in a stuporous condition. She had felt quite well until a few days before when she had a severe attack of pain in the epigastrium. This came on very suddenly and she was "doubled up" with the severity of it. She had not urinated and had not had any bowel movements for 2 days before coming to the hospital. There was some pitting edema of the extremities. Her pulse rate was 120 and of poor quality. The blood pressure was 70 to 80 mm. Hg systolic. The leukocyte count was elevated. The urine contained albumin and casts. The next day her condition was worse. She became more cyanotic, respirations were labored and the lungs filled up with fluid. That evening she died quite suddenly. The heart rate a few minutes before death was 120. No autopsy was obtained.

CASE 7.—B. R., male, aged 72 years, entered the hospital April 13, 1932 on Dr. I. Koll's service, with a hematuria. This was found at cystoscopic examination to be due to a papilloma of the bladder. Some hours after this examination the patient suddenly became very ill with symptoms typical of a coronary accident. He had pain, vomiting, increased temperature, a fall in blood pressure, and a leukocytosis of 16,600. The pain was present for several days, but he gradually improved and in several weeks was discharged from the hospital.

CASE 8.—F. N., male, aged 62 years, for about 10 years had complained of a feeling of pressure in the precordial area which usually came on after meals. One week before entrance into the hospital he began to have extreme pain which radiated to the left arm. On the day of a severe attack (April 27, 1932), he was sent into the hospital by Dr. Sidney Strauss with clinical symptoms typical of a coronary accident. He gradually improved but had occasional attacks of tachycardia. When discharged a month after admission he was free from pain.

CASE 9.—L. F., male, aged 60 years, about 1 month before entering the hospital was suddenly seized with a severe pain in the epigastrium which almost immediately radiated into the precordial area. This was accompanied by a sense of constriction across the anterior thorax and a choking feeling in the throat. Following rest in bed and medication the patient felt entirely well in a few days and went back to work. Two weeks later he had another attack, and from that time until entrance into the hospital he had repeated attacks of pain usually relieved by nitrites. He was sent into the hospital by Dr. W. Hamburger on October 1, 1931. He improved steadily during his stay in the hospital and was discharged improved after a few weeks.

CASE 10.—A. G., male, aged 75 years, 3 days after the extraction of a tooth had a severe attack of epigastric pain radiating to the left arm and shoulder. The pain was very severe. He became acutely ill, had nausea

and vomiting and received no relief from any medication. Twenty-four hours later he was sent into the hospital by Dr. Sidney Portis (October 30, 1931). At this time his blood pressure was 110 mm. Hg systolic, and 70 mm. Hg diastolic; his temperature was 102° F., and his leukocyte count was 14,450. He was kept in bed, and after a month was discharged.

CASE 11.—M. F., male, aged 12 years, was under observation in the Children's Cardiac Clinic, for 3 years before entrance to the hospital. He had definite rheumatic pain and heart disease was suspected, although it was a year after the pain started before a definite cardiac murmur to the left of the sternum was heard. The child gradually became worse following the appearance of this murmur, and the murmur grew rapidly louder and more definite. He was sent into the Sarah Morris hospital on January 11, 1932, on Dr. J. Gerstley's service, acutely ill. Positive blood cultures for *Streptococcus viridans* were obtained, and in a few days he died following emboli in the left popliteal and left axillary arteries. At autopsy there was found an acute ulcerative and vegetative endocarditis of the aorta and mitral valves superimposed upon a chronic rheumatic endocarditis. There was an insufficiency of the aortic valves and an acute myocarditis.

Summary and Conclusions. Electrocardiograms are presented of 10 cases having a clinical history typical of protracted or transient coronary occlusion of recent origin.

The most significant findings in cases of recent coronary occlusion are changes in the form of the *S-T* segment and the *T* wave: either an elevation, a depression, or an inversion. The most significant fact is that a definite change is present, whether it be in an upward or in a downward direction. Successive records usually show a rapid change in contour in the early stages of coronary occlusion. Not all curves in recent coronary cases can be fitted into the *T*₁ and *T*₃ types of Parkinson and Bedford.

Attention is drawn to a large, upright, sharply peaked *T* wave whose limbs and shoulders are symmetrical and have their convexity pointing downward and toward each other, associated with an isoelectric or negative *S-T* interval having a "hump" pointing down. It is different from the non-specific, tall *T* wave. This large, upright *T* wave is most commonly found in Leads II and III of the *T*₁ type and is as diagnostic a feature of the coronary occlusion type of curve as the inverted cove-shaped *T* wave of which it is the inverse image. We have designated this characteristic as the upright coronary *T* wave.

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SPECIFIC SERUM TREATMENT OF TYPE I LOBAR PNEUMONIA.

REGULATION OF DOSAGE BY THE OBSERVATION OF CIRCULATING AGGLUTININS WITH THE STAINED SLIDE AGGLUTININ TEST. (SABIN.)

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RECOVERY from lobar pneumonia due to pneumococci has been shown to be associated with the appearance of humoral antibodies against the specific type of pneumococcus responsible for the infection. Neufeld¹ suggested that the demonstration of humoral antibodies might be used as an indication of the proper dosage of antipneumococcic immune serum in the treatment of pneumonia. Cole,² Sutliff,³ and Sabin^{4,5} have reported the demonstration of type specific agglutinins during the course of treatment with immune serum. We have attempted to determine the minimum dosage of antipneumococcic immune serum necessary to produce demonstrable agglutinins in the patient's blood and to correlate this with the therapeutic result. The technique used is that described by Sabin⁴ and is simple enough to be carried out with a minimum of apparatus and labor. Its use resulted in the administration of less serum, thus sparing the patient some discomfort and expense. It is recommended to physicians who desire to control antipneumococcic serum administration carefully.

Materials and Methods. Twenty-four patients were studied less than 96 hours after the onset of Type I pneumococcic lobar pneumonia. Twelve

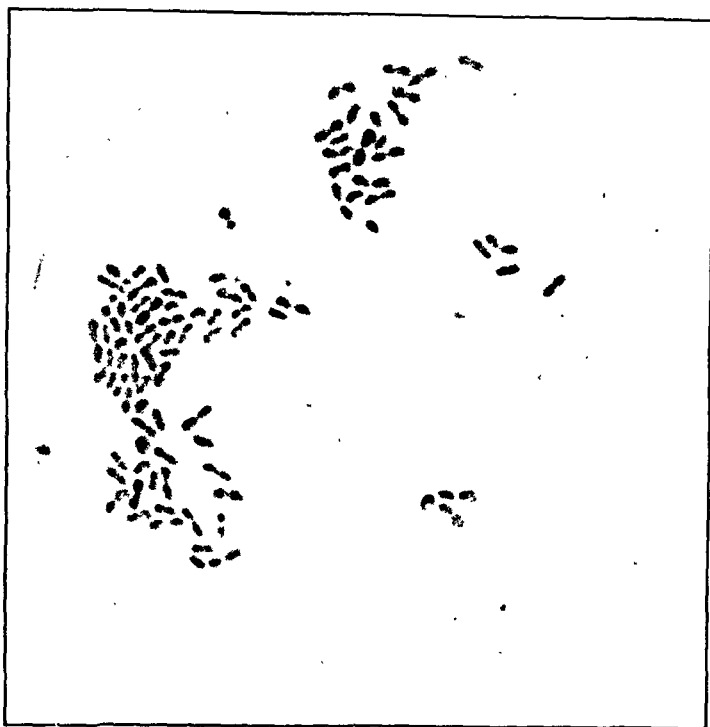
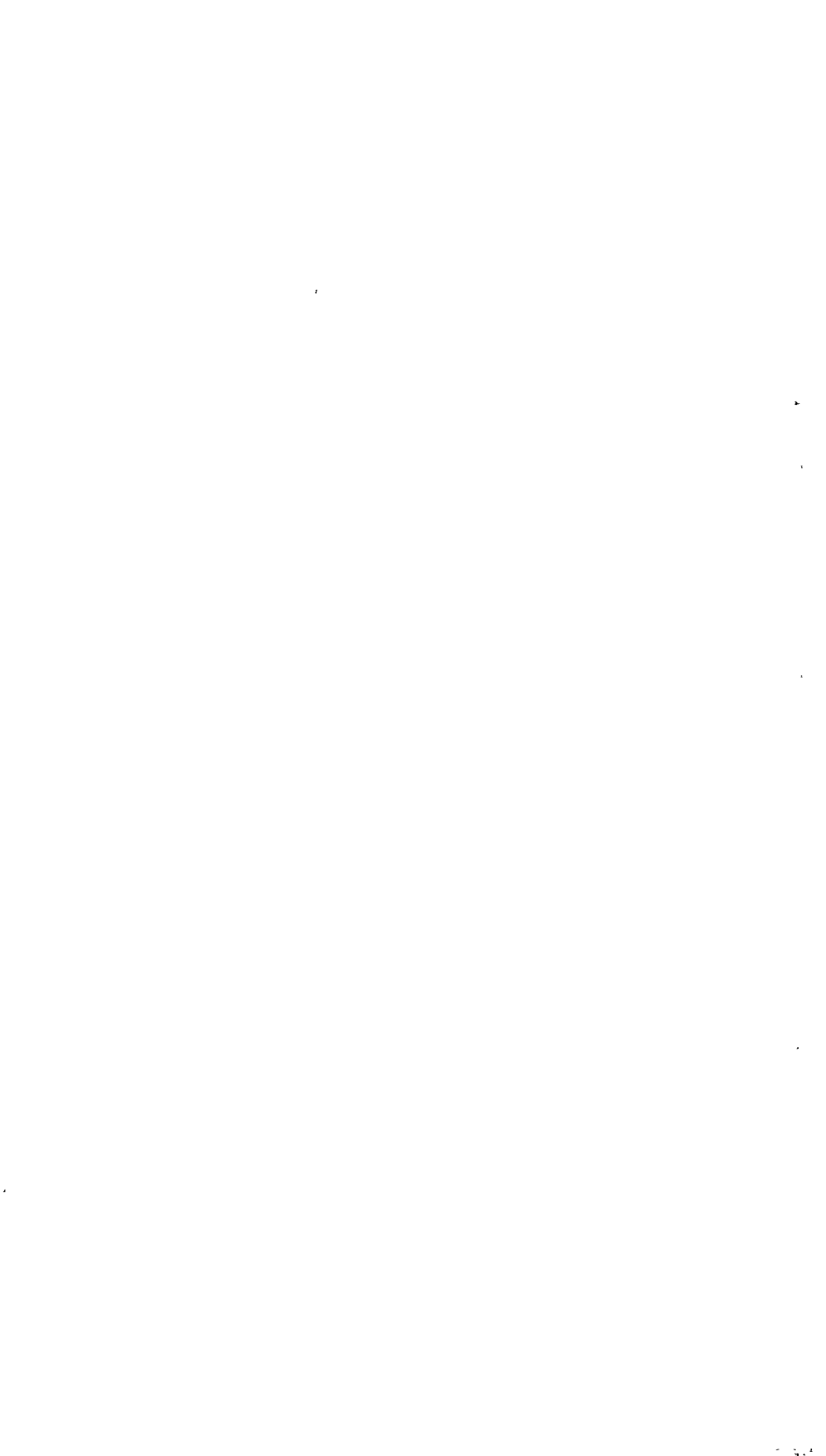


FIG. 1.—Positive agglutination of Type I pneumococci in patient's blood. (Oil immersion $\times 1800$.)



FIG. 2.—No agglutination of Type I pneumococci in patient's blood. (Oil immersion $\times 1800$.)



were treated as follows: The serum used was polyvalent concentrated antibody prepared by Felton's method, specific for Types I and II, and was supplied by the State Antitoxin and Vaccine Laboratory. Treatment was begun as soon as practicable after the determination of the type of the infecting organism. Blood was obtained for culture and agglutinin study before beginning treatment, at frequent intervals during therapy, and for some days following recovery. The serum was given in doses of 5, 10, or 15 cc. containing 2500 mouse protective units per cc. Twenty-five cc. were given during the first 4 hours (except in Case 12) but subsequent doses were given only when homologous type agglutinins were not demonstrable in the blood of the patient by the slide method. Agglutinin tests were made at 2-hour intervals on the first day of treatment and at 4-hour intervals thereafter as long as the patient showed signs of toxicity. Following symptomatic recovery, studies were made at daily or longer intervals to demonstrate the duration of the persistence of agglutinins. Twelve other patients were treated with a standard, empirically derived dosage of 75 cc. or more of the same serum.

The technique of determining the circulating antibodies in these observations was similar to that described by Sabin.⁵ Two drops of blood, about the size of a drop from a 3 mm. platinum wire loop, obtained by puncture of the finger tip or ear lobe, were placed on a glass slide. By means of the platinum loop an equal amount of Type I pneumococcus antigen was quickly mixed with 1 drop of blood, and a similar sized drop of Type II pneumococcus antigen was mixed with the other. These mixtures, kept separate, were spread thin and allowed to dry. This can readily be done at the bedside using an alcohol lamp to flame the wire. The smears were then stained with 0.1 per cent aqueous safranin to which a few drops of 10 per cent acetic acid were added to hemolyze red blood corpuscles and examined under the oil-immersion lens. Agglutination, when present, was quite characteristic and easily recognized, the organisms being gathered in clusters of a definite pattern. Negative tests showed the organisms spread out uniformly over the slide (Figs. 1 and 2).

The antigens were prepared from an 8-hour growth of a culture of maximum mouse-virulence by washing twice in physiologic saline, and resuspending the organisms in saline to which 0.5 per cent of formalin was added.

Two cases (Cases 9 and 11) are described here to illustrate the course of treatment and the response to small doses of serum as administered on the basis of type-specific agglutinin determination. The charts show the relation of body temperature, blood culture, and circulating antibody to treatment.

Type Cases. CASE 9 (Fig. 3).—J. P., aged 35, white male, entered the hospital on April 6, 1932, 37 hours after a chill which marked the onset of his illness. He was in moderate distress, somewhat dyspneic, and cyanotic. Physical and Roentgen ray signs revealed consolidation of the right lower lobe. Sputum examination revealed pneumococcus Type I. Blood culture was negative on the day of admission, but showed pneumococcus Type I, just prior to treatment. Serum treatment was begun the following morning, 50 hours after the onset, the dosage being regulated by the presence or absence of agglutinins in the patient's blood as detected by the slide method. Agglutinins were found to be present after the second dose, a third dose being given at this time, making 25 cc. in all. Agglutinins were found to be present when sought at 2-hour intervals following treatment for 12 hours. There was a prompt drop in temperature with marked subjective improvement the following morning. Blood culture was negative at that time. The agglutination test after 24 hours left one in doubt as

to whether or not agglutinins were present, so a further dose of 10 cc. of serum was administered. Agglutinins for pneumococcus Type I were found to be present thereafter for 5 days while the presence of agglutinins for pneumococcus Type II was doubtful 48 hours after the last dose of serum and they were definitely absent after that. The temperature remained normal and the patient experienced a rapid and uneventful convalescence. No agglutinins were demonstrable in his blood either by the microscopic slide method or the macroscopic tube method 12 days after the last dose of serum.

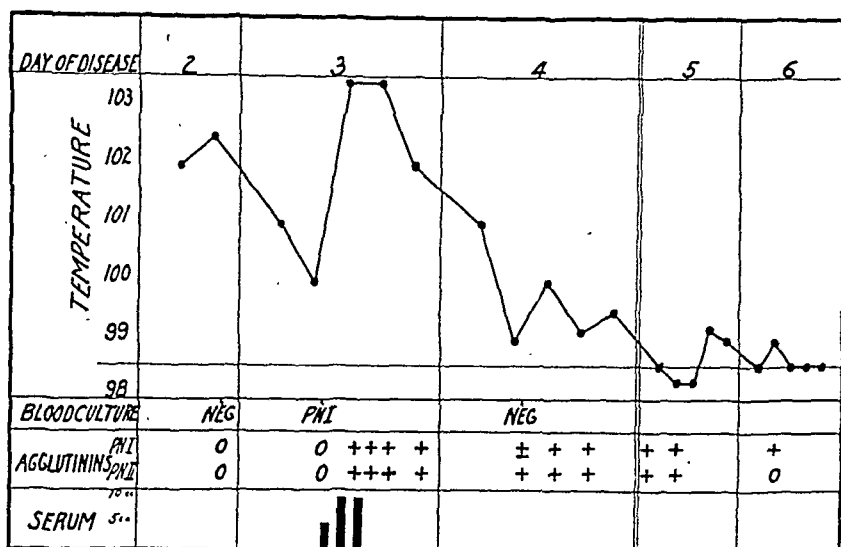


FIG. 3.—Case 9. Treatment begun on second day of disease; prompt recovery after 35 cc. of serum. PNI = Pneumococcus Type I.

This case is quite typical of many serum-treated patients because immediately after the administration of serum there was a rapid drop in temperature, clearing of the blood-stream infection and marked general improvement, subjectively and objectively. Five of the 12 cases showed this type of response after receiving total doses of from 15 cc. to 45 cc. of the concentrated antibody intravenously.

CASE 11 (Fig. 4).—R. R., aged 39, white, male musician, was admitted to the hospital on April 21, 1932. He had been well until 39 hours before admission when he was suddenly seized with a stabbing pain in the right lower chest which radiated to the upper abdomen. He felt very ill and feverish. About 4 hours before admission there was a sudden severe exacerbation of the pain in the upper abdomen; the pain continuing for 1 hour and gradually diminishing to the time of admission.

Physical examination revealed a well-developed, slightly undernourished white man, obviously very ill. The skin was hot and dry, the face and extremities slightly cyanotic. Respirations were rapid, short and jerky, accompanied by pain. There was an occasional hacking cough with a moderate amount of tenacious, yellowish sputum. The thorax revealed dullness to percussion with relative diminution in the intensity of the breath

of which pneumococcus Type I was obtained on culture. He recovered completely after appropriate surgical treatment.

This case is presented to show the phenomenon of absorption of the homologous agglutinins contained in the therapeutic serum when administered in the doses used in Case 11. It is interesting to note that while the agglutinins for pneumococcus Type I appeared and disappeared 5 times during the period of treatment agglutinins for pneumococcus Type II persisted except at the time the pneumococci returned in the blood the day after treatment was begun. Serum was given to this patient only when the slide agglutination test indicated the absence of agglutinins in his blood. By comparison with Case 9 it is seen that the serum requirement of these 2 patients varied within wide limits.

TABLE 1.—PATIENTS WITH TYPE I LOBAR PNEUMONIA TREATED WITH SPECIFIC SERUM ON BASIS OF AGGLUTININS IN BLOOD.

Case No.	Age, years.	Duration of disease to admission, hrs.	Duration of disease to onset of treatment, hrs.	Blood culture before treatment.	Total dosage serum, cc.	Duration from treatment to first sustained drop in temperature, hrs.	Duration from treatment to complete symptomatic improvement, hrs.	Result of treatment.
1	74	28	41	Pn. I	55	19	..	Died on 11th day; no pneumococci in cultures at autopsy.
2	63	In hosp.	24	Neg.	45	15	43	Prompt recovery.
3	27		26	Neg.	55	13	..	Empyema; recovered after thoracotomy.
4	46	55	84	Neg.	55	6	134	Prompt recovery; sterile subcutaneous abscess.
5	26	60	79	Neg.	25	19	72	Prompt recovery.
6	22	62	71	Neg.	35	164	212	Delayed recovery.
7	45	32	51	Neg.	25	19	47	Prompt recovery.
8	37	63	74	Neg.	40	55	107	Delayed recovery; delirium tremens.
9	35	37	50	Pn. I	35	23	31	Prompt recovery.
10	30	23	45	Pn. I	55	17	..	Delayed response; Strep. empyema; died; no pneumococci in cultures at autopsy.
11	42	39	63	Pn. I	105	45	141	Delayed response; empyema, recovered after thoracotomy.
12	36	51	80	Neg.	15	15	112	Prompt recovery.
Average	40	57	57	..	45	34	100	

Two tables are presented here to compare the results obtained by use of small doses of serum controlled by the agglutinin method

with the results obtained by using large doses of serum. Analysis of Table 1 reveals that 7 of the patients treated on the basis of the presence or absence of agglutinins recovered without complications, 5 promptly and 2 after a slightly delayed course. Two patients (Cases 1 and 10) died, 1 from a secondary streptococcus infection after apparent recovery from pneumonia (reported by Parsons and Myers¹⁸). Beta hemolytic streptococci were found in the lungs of each of these patients at autopsy, but no pneumococci were demonstrable. No further deaths occurred in the series, making the rate 16 per cent for this group of 12. Due to the small number of cases this has slight if any significance. Two patients (Cases 3 and 11) developed empyema due to pneumococcus Type I and recovered after thoracotomy and tidal irrigation. One patient (Case 4) developed a sterile abscess on the right arm at the site of a hypodermic injection which apparently was responsible for fever during his convalescence.

TABLE 2.—PATIENTS WITH TYPE I LOBAR PNEUMONIA TREATED WITH EMPIRICAL DOSE OF 75 CC. OR MORE OF SPECIFIC SERUM.

Case No.	Age, years.	Duration of disease to admission, hrs.	Duration of disease to onset of treatment, hrs.	Blood culture before treatment.	Total dosage serum, cc.	Duration from treatment to first sustained drop in temperature, hrs.	Duration from treatment to complete symptomatic improvement, hrs.	Result of treatment.
13	37	53	79	..	75	10	14	Prompt recovery.
14	52	68	86	..	75	18	118	Delayed recovery (serum sickness).
15	45	55	72	Neg.	75	8	120	Prompt recovery (serum sickness).
16	42	57	80	Neg.	75	63	71	Delayed recovery.
17	37	49	66	Neg.	75	8	72	Prompt recovery.
18	24	69	77	Neg.	75	12	64	Prompt recovery.
19	15	72	83	..	75	18	18	Prompt recovery.
20	52	24	48	..	75	0	45	Temperature dropped before treatment begun.
21	24	48	72	Pn. I	120	21	..	Empyema; recovered after thoracotomy.
22	38	77	95	..	75	6	6	Prompt recovery.
23	25	11	28	Pn. I	75	0	23	Temperature dropped before treatment begun.
24	35	48	70	..	75	47	47	Delayed recovery.
Average	36	52.5	71	..	79	18	54	

Table 2 shows that of the 12 patients treated with large empirical doses (75 cc. or more according to clinical condition of patient) 6 recovered promptly and 3 recovered without complications after

a delay of 2 or more days following serum administration. Two patients in this group had a drop in temperature before serum therapy was begun, suggesting spontaneous recovery. One had empyema due to pneumococcus Type I and recovered after thoracotomy and drainage. None of these patients died.

The duration of the disease to the first sustained drop in temperature was less than 23 hours in all but 3 patients (Table 1), with an average of 34 hours. In Table 2 the duration was less than 21 hours in all but 2 patients, with an average of 18 hours. On com-

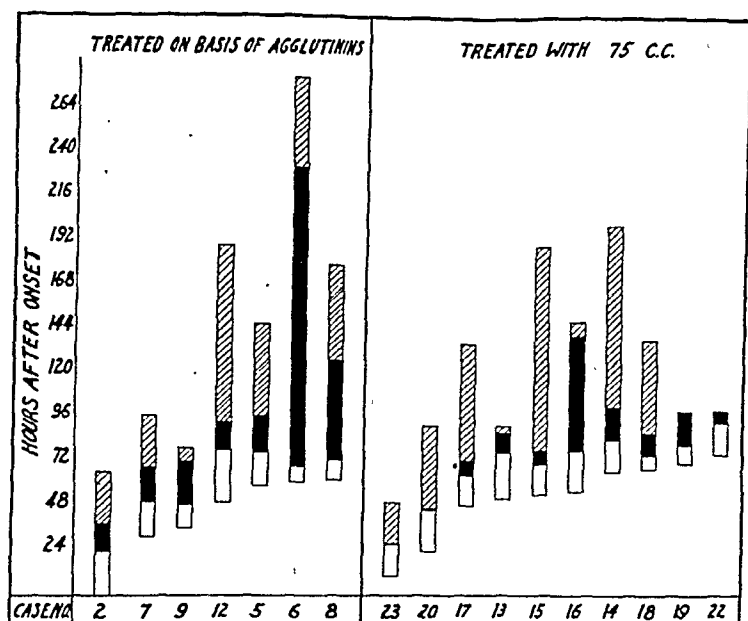


FIG. 5.—Duration of the disease in agglutinin controlled and empirically treated cases. Each bar represents 1 patient who had an uncomplicated course ending in recovery. The distance of the bar from the base line represents the duration of the disease before entry, the light portion the duration from entry to serum administration, the solid portion the duration to the first sustained decrease in temperature below 101° F., and the hatched portion the duration to the disappearance of all symptoms and fever.

paring this with the results in a similar series of specifically treated patients in which 17 of 18 showed a symptomatic response within 30 hours after treatment (Sutliff and Finland¹⁷), it is seen that the therapeutic effect in the present series was probably satisfactory in both groups of patients. The average duration of the disease is much shorter for the patients in Group II, who received larger doses of serum than in Group I, but, in view of the experience with this same method of treatment quoted above,¹⁷ such an extraordinarily rapid average response cannot be expected to occur when more cases are included.

Figure 5 represents in graphic form the duration of the disease to admission, to onset of treatment, to initial sustained drop in temperature and to complete symptomatic recovery from the disease for the uncomplicated, recovered cases in the two groups of serum-treated patients.

Comparison of the total dosage used to treat the cases recorded in Table 1 with the amount used to treat the cases recorded in Table 2 shows that there was a considerable saving in the amount of serum used. The average amount for those patients in whom the dosage was regulated by the presence of agglutinins was 45 cc.; for those treated empirically the average amount was 79 cc. The amount of serum required to produce demonstrable circulating agglutinins in the 12 patients with lobar pneumonia due to pneumococcus Type I varied from 15 cc. to 105 cc. Most of these patients required from 25 cc. to 55 cc. to produce this effect.

Discussion. That specific antibodies play an important rôle in recovery from infectious diseases has been conjectured since the earliest days of the bacteriologic era. The reader is referred to the paper by Bailey⁷ for a detailed analysis of the theory of agglutination and the part it plays in recovery from disease.

The appearance of circulating humoral antibodies in the blood of patients convalescent from lobar pneumonia was first demonstrated by Klemperer and Klemperer⁸ who showed that the serum of such patients protected rabbits from otherwise fatal doses of pneumococci. Neufeld and Händel⁹ pointed out that this protection was specific for the type of pneumococcus causing the pneumonia, that it appeared about the time of recovery and that specific agglutinins were present in the same blood samples. Dochez¹⁰ found antibodies protective for mice against the homologous serum. Clough¹¹ found phagocytosis to be enhanced by homologous convalescent serum.

Cole¹² in presenting a series of studies on patients treated with antipneumococcic immune serum noted the occurrence of similar antibodies in the patients' blood after the injection of serum. Lord and Nesche¹³ followed the mouse protective antibodies and agglutinins in a series of serum treated and a series of non-specifically treated patients. They found agglutinins to appear in 7 treated patients before demonstrable protective antibodies appeared and from this they concluded that the appearance of agglutinins would be a dangerous criterion on which to base the administration of serum. Finland and Sutliff,¹⁴ on the other hand, have stated that protective antibodies are generally more readily detected than agglutinins and that in cases of Type I and II pneumococcic pneumonia agglutinins are not demonstrable in the absence of protective antibody. Sia, Robertson and Woo¹⁵ found the power of whole fresh blood to kill virulent pneumococci, which is acquired during the course of lobar pneumonia, to be present in all cases where agglu-

tinins are demonstrable. Felton¹⁶ in discussing the various antibodies in antipneumococcic immune serum states that “. . . attempts to separate the water insoluble proteins into fractions . . . have failed to disclose . . . fractions in which any . . . antibodies are separated. Thus one fraction containing the protective substance can be shown to contain the other immune reactions.”

On the basis of the foregoing facts we are led to the assumption that where agglutinins are demonstrable protective antibody is present and that its persistence in the circulating blood indicates an excess, no matter how small, of the antibody needed to terminate the infection. The phenomenon of the absorption of antibody, first noted by Cole,² is evidence of the quantitative utilization of immune bodies by the infected individual. This phenomenon is admirably illustrated in Case 11, in which it is seen that the homologous agglutinins repeatedly disappeared some hours after the serum was administered as though neutralized. The Type II agglutinins, heterologous to the infecting organism, which were present in the therapeutic serum were found to persist. It is apparent that homologous agglutinins were present in the patient's blood only after he had received an excess of serum. A similar observation, less pronounced, is made in Case 9.

The slide agglutination method seems to be a practicable and effective method for determining the amount of serum to be administered, an amount which varies between wide limits. Hitherto it has been customary to determine the dosage of antipneumococcic serum by “the condition of the patient,” a vague reliance on clinical judgment. Under such a therapeutic scheme there is grave danger that a patient may receive too little serum as the result of a temporary amelioration of symptoms. It is well known that following the administration of immune serum there may be misleading signs of recovery with subsequent relapse unless the therapy is continued. An empirical dose large enough to cover all cases effectively would entail for the majority of patients a great waste of an expensive pharmaceutical product. Serum sickness, which is more common among patients receiving large than small doses of antibody, may be avoided in a certain number of cases when doses no larger than necessary are given.

These observations, it is emphasized, were made on patients treated early in the course of the disease. It is not known whether these results would obtain in patients in whom the disease had existed for a longer period.

Summary and Conclusions. The effectiveness of two methods of dosage of specific serum in the therapy of pneumococcic Type I lobar pneumonia is compared in two groups of 12 cases each, treated before the 5th day of their disease. In the first group amounts of serum were given (15 to 105 cc., average 45 cc.), just sufficient to

maintain agglutinins in the circulating blood, as determined by a rapid bedside method. In the second group a larger, empirically selected dose (75 cc. or more, average 79 cc.) was given to each patient.

In both groups the response to the therapy was satisfactory as shown by the short duration of the disease after therapy, and by the death rate. On the average, the course of the disease in the 12 empirically treated patients was much shorter than the average course of a larger series of cases treated in the same manner, but this unusual result in a small series of cases does not necessarily indicate the superiority of this method of therapy.

Evidence is given to indicate that the persistence of agglutinins for the homologous organism is an index that a sufficient amount of antipneumococcic serum has been administered to produce a satisfactory therapeutic result.

The authors are indebted to Dr. Claude E. Welch for assistance.

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SEASONAL INFLUENZA.

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UNTIL the agent immediately responsible for influenza is discovered, no specific diagnostic procedure for identification of the disease is likely to become available. Its recognition on purely clinical grounds, however, is easy enough in the midst of epidemics

such as occurred in 1830, 1836, 1847, 1889 and 1918. Whether or not the sporadic cases commonly encountered at other times and called by some name as La Grippe, grip, or pseudo-influenza are really due to the same etiologic factor cannot be determined with certainty at this time. In both, the Pfeiffer bacillus is frequently found, but today few believe it to be the exciting cause. To say that both are due to a filtrable virus means nothing so long as the specific virus is undetermined. The decision for the present must rest on clinical grounds.

From a description of the disease as it occurred in the epidemics we may conclude that influenza is an acute febrile illness of unknown etiology, sudden in onset, and generally attended by headache, backache and pains in the extremities; catarrhal symptoms are frequent; the duration usually short, although frequently followed by prostration, and there is a notable tendency to pneumonia. In addition to this more or less general description of the disease, there are other characteristics brought out in a study of the individual case. The period of incubation is usually between 24 and 48 hours; the onset is not only sudden, as a rule, but the patient is frequently able to recite the exact moment when he was taken ill (Stengel¹). A slow or disproportionate pulse is frequent and cyanosis often a characteristic. A low diastolic pressure is reported by one observer (Riesman¹). One feature of influenza which is usually present and upon which great stress is laid in diagnosis, is the leukopenia that occurs in the disease. Bronchopneumonia is the most frequent serious complication and is usually spoken of as influenzal pneumonia because of the atypical signs of the disease and protracted course with persistent cough often simulating tuberculosis (Landis¹). Other frequent complications are sinusitis, otitis media and various psychoses. The tonsils are said to be an important focus of infection in influenza (Davis¹). Immunity, if it exists at all, is probably of very short duration. Any natural immunity that may have been present is easily lost if the individual's resistance is lowered.³ Acquired immunity is disproven by the patients who had several attacks of the disease in the 1918 epidemic.⁴

The epidemiologic characteristics of influenza are important, because on these the diagnosis is chiefly based.⁵ First, the great explosiveness of the disease, rapid increase in the number of cases in a community reaching a peak in 2 to 3 weeks and gradually fading in about the same length of time. Next, the high dispersiveness or rapidity with which the disease spreads from place to place. Other characteristics are: the high morbidity with low case fatality; independence of weather and season; the increased death rate among young adults, a robustness of temperament being almost a predisposing factor; and lastly the recurrence of epidemics of the disease.

Between these pandemics of influenza there occur every year

during the winter months localized outbreaks of an acute febrile disease varying in intensity from year to year and having many of the characteristics of epidemic influenza. Many observers have noticed the similarity of this seasonal disease and epidemic influenza, but concluded that they were not the same.^{1,2} Parsons,⁶ in 1891, expressed the view of the dissimilarity of the two diseases and based his belief largely on the mortality in the several age groups: the high mortality of influenza in young adults was apparent in epidemics of the disease. The pandemic form of influenza is said to differ in the greater explosiveness and more rapid spread of the disease; catarrhal symptoms are less frequent; mental depression more marked; pneumonia more frequent and of a different type; greater and more prolonged prostration following the acute attack; leukopenia more common, and the incidence and mortality of the disease higher, especially in young adults.

Our knowledge of the life history of influenza between pandemics is very meager and so long as we are ignorant of the causative organism it will be difficult to recognize sporadic cases. It may be that there are different strains of the influenza organism and that this organism is with us always¹⁰ and is capable of a change of virulence which may account for the pandemics of the disease from time to time.⁵ The endemic cases of influenza which are caused by the less virulent organism occur during the winter months when our resistance is lowest and epidemiologic factors most favorable. When these seasonal outbreaks are investigated, many of the characteristics of so-called true influenza become more apparent. Miller⁸ reported a group of cases which occurred at the University of Oregon in November and December of 1928. There were 319 cases, 250 of which were hospitalized. In this group there were 9 complications; 4 of which were pneumonia, 3 of these being the so-called typical influenzal bronchopneumonia; 3 cases of otitis media; 1 of follicular tonsillitis; and 1 antrum infection. There was 1 death. The disease as reported resembled very much the influenza as seen in pandemics, the chief difference being in the severity of the infection.

To illustrate what was perhaps a typical outbreak of seasonal influenza, a group of 140 unselected cases was collected from the records of the Student Health Service of the University of Pennsylvania for the school year 1931, 1932. A similar outbreak occurred in 1930, 1931, and a more severe one in 1929, 1930. All of the cases referred to in the report were in students between the ages of 17 and 27 years, and all were confined to the infirmary of the Student Health Service. The cases, 124 in males and 16 in females, occurred among the 5800 students eligible for treatment in the Health Service. The first case was admitted December 8, 1931, and the last one was discharged June 22, 1932. The onset was usually sudden, frequently characterized by coryza or other catarrhal

inflammation of the upper respiratory tract; within 12 to 24 hours pains in the extremities developed, and in many cases pains in the eyeballs; the temperature during the first day rose gradually to its peak, which averaged 100.9° F. in the 128 uncomplicated cases. In only 49 of these uncomplicated cases did the temperature ever exceed 101° F. and in 8 instances it reached 103° F. The duration of the fever in the uncomplicated cases averaged 2.9 days and usually terminated by lysis. During the illness the patient as a rule did not appear very sick, his complaints were few, and frequently his symptoms did not warrant his temperature. It was often difficult to convince the student that he should be confined to bed. In other words, the disease lacked the great prostration shown in the epidemics. Cyanosis¹ and the peculiar flushed appearance of the countenance sometimes associated with the disease did not occur. The patients were not mentally depressed. No noticeable effect on the cardiovascular system was observed. In the average case the pulse rate was proportionate with the fever. The average pulse pressure was 42.6, with a normal blood pressure for this age group being about 120 systolic and 80 diastolic. Of the 42 cases that showed positive urinary findings, only albuminuria, usually a trace, and occasionally a trace of sugar, were noted. This would be expected in any group of acute infectious fevers. No case of nephritis developed.

The most important confirmatory evidence of the diagnosis of influenza was in the white blood cell count. In 70 per cent of the uncomplicated cases the white cell count was less than 7000 and in 12 of the 15 cases in which the count was 10,000 or more some complication, as bronchopneumonia, could be demonstrated. The average white cell count in uncomplicated cases was 5400. The connection between the white blood count and the course of the disease was studied. No appreciable relationship existed between the white cell count and the degree of fever. The average maximum temperature for uncomplicated cases in which the count was 7000 or over, was 101.3° F., as compared with an average temperature of 100.9° F. for all uncomplicated cases. The duration of fever was little affected by differences in cell count. The average duration of fever for cases with cell count less than 7000 was 2.8 days, as compared with 3.2 days in cases with a cell count of 7000 or over. Another similarity between this group of cases and the influenza as seen in the epidemics was shown in the complications that developed. The most frequent serious complication of epidemic influenza is bronchopneumonia. In this group there were 12 with complications; 6 with bronchopneumonia; 3 with otitis media; 2 with follicular tonsillitis, and 1 with maxillary sinusitis. The bronchopneumonia presented indefinite signs and in 2 cases the persistent chest findings and cough made it difficult to rule out tuberculosis.

The contagiousness of the disease was considered. In one dormi-

tory in which there were 43 students only 6 developed the disease. Most of these students had separate rooms and, when the patient had been living with another student, his roommate showed no special tendency to develop the disease. In another dormitory accommodating 37 students 5 cases occurred. In still another, 5 out of 29. All of the 16 girls who contracted the disease lived in one dormitory, in which there were 150. The presence of tonsils was investigated as a possible predisposing cause. In 70 per cent of the cases in this group the tonsils had been removed. The question of immunity conferred by previous attacks of influenza was considered and an attempt made to determine this from the history. In the 63 cases in which a definite history could be obtained, 46 had never had influenza before, 18 had, 2 of these having had the disease twice before.

Conclusions. In the absence of some positive criterion for the diagnosis of influenza the characteristic acute febrile illnesses occurring every winter should be regarded as influenza.

The chief points of similarity are: the "explosiveness" and "dispersiveness" of the two diseases; the high incidence in young adults; the sudden onset and short duration; general symptoms; leukopenia; and the frequent complication of an atypical bronchopneumonia.

The seasonal influenza, as it may be termed, is probably due to a milder strain of the influenza organism, which accounts for the comparative mildness of the disease. The virulence of the organism causing seasonal influenza may increase, and under favorable circumstances give rise to pandemics of influenza.

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CHRONIC ADRENAL INSUFFICIENCY: AN HITHERTO UNDESCRIBED SYNDROME: WITH CASE REPORT.*

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ALTHOUGH great advances have been made in our knowledge of the pathology and pathologic physiology of the adrenal glands, their possible function and relation to the other organs of the body, are still largely matters of conjecture. Perhaps the recent isolation of active cortical extracts will solve the riddle and with it a host of correlated questions, such as their relationship to Addison's disease, to appetite, to malnutrition and to vitamin B. Clinical cases in which the lesion is apparently primary in the suprarenals, can often shed some light on these problems. We believe that the following case, with its unique clinical syndrome and its unusual etiology, serves such a rôle.

Case Report. E. S., male, Hungarian, aged 50 years, was admitted to the medical service of this hospital November 30, 1931. Because of language difficulties and the lack of coöperation on the part of the patient, the history was unsatisfactory. Upon inquiry, he admitted that he had not eaten any food for a week and that his diet had been inadequate for several months previously. Nothing could be elicited about his past history, except that he had been in Bellevue Hospital on several occasions for acute alcoholism.

Physical Examination. Temperature, 96° F.; pulse, 70; respirations, 20; blood pressure, 148 systolic and 80 diastolic.

He was greatly undernourished and looked acutely ill. His face had a grayish pallor and an anxious expression. A marked anasarca of the entire torso and all four extremities was present, most pronounced in both lateral thoracic regions. The face and neck were not involved. The mucous membranes were pale. A cataract was present in the right eye, the left was normal. There was impaired resonance over the left apex of the lung and absolute flatness below the third rib anteriorly and the spine of the scapula posteriorly. Over the apex, tubular breath sounds and a few moist râles were audible. Breath and voice sounds and fremitus were absent over the area of flatness. The right lung was hyperresonant. The apex beat of the heart was neither visible nor palpable. The borders could not be determined. The sounds were of poor quality but no murmurs were audible. The pulses were equal, regular and the radial walls were somewhat thickened. The abdomen was negative. The prostate felt moderately enlarged, smooth and firm. The reflexes were normal.

Laboratory Reports. Red blood cells, 4,150,000 per c.mm.; hemoglobin, 84 per cent (Sahli); white blood cells, 11,300 per c.mm.; neutrophils, 85; lymphocytes, 12; mononuclears, 2 per cent. Urine: Cloudy amber;

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specific gravity, 1.022; reaction, acid; sugar, negative; albumin, negative; an occasional hyalin and granular cast, a few leukocytes and no red blood cells. The blood Wassermann reaction was negative. The cerebrospinal fluid was normal. It contained no cells and no globulin. Wassermann and colloidal mastic tests were negative. Chemical examination of the blood plasma showed non-protein nitrogen, 37 mg. per cent; sugar, 123 mg. per cent.

An electrocardiogram showed slurring of the *Q-R-S* complexes and flattening of the *T* wave in Leads I and III.

Roentgen rays of the chest revealed obliteration of the left pulmonic field from apex to base and a large, dense, sharply circumscribed shadow near the hilus of the right lung.

Course. He was put on a high caloric, vitamin B-rich, salt-poor diet. Fluids were limited to 1000 cc. and he received one injection of salyrgan. Two days after admission, 2030 cc. of straw-colored fluid with the characteristics of a transudate were aspirated from the left chest. Tumor cells or tubercle bacilli could not be demonstrated. A roentgenogram taken after the aspiration showed a persistence of the mass in the right chest and bronchoscopy was then performed with entirely normal findings. Roentgen rays of the long bones, skull and gastro-intestinal tract were negative.

The patient ate voraciously and a remarkable improvement in his general condition was soon noticeable. He became mentally alert, jovial and active. The edema began to perceptibly diminish on the fourth day after admission and had entirely disappeared by December 14. The mass near the hilus of the right lung also vanished and Roentgen ray (December 17) revealed nothing but some interlobar pleural thickening in this region. Repeated urinalyses were normal. His blood pressure rose to 178 systolic and 100 diastolic. His blood count at this period was red blood cells, 3,750,000; hemoglobin, 68 per cent; white blood cells, 8100; neutrophils, 78; lymphocytes, 18; mononuclears, 3 per cent.

The improvement, however, lasted for but 10 days. Quite suddenly his voracious appetite was superseded by profound anorexia and rapid and astounding emaciation. The progressive deterioration was accompanied by marked asthenia, melancholia and desire for death. He became very tremulous and involuntary athetoid movements in the fingers were noted. The superficial and deep reflexes disappeared entirely with the exception of the left plantar reflex. Joint sensation was universally impaired and there was loss of perception of touch and pain in the extremities. For a short time, a slight left facial weakness was present. A few days after these observations, he began to complain of severe burning pains in all the extremities, and their muscles and nerves were extremely tender.

By the early part of January, in spite of forced feedings and glucose and calcium gluconate intravenously, the appearance of the patient was truly cadaveric. He was semi-stuporous, irrational when aroused and incontinent of both urine and feces. The athetoid movements persisted. *The panniculus adiposus had universally and completely disappeared.* The eyeballs and cheeks were sunken, the bony borders of the chest and abdomen and the muscles of the extremities (especially the abductors of the thighs and the flexors of the forearm) were prominent and the abdomen was markedly scaphoid. In spite of the extraordinary wasting, the skin retained its elasticity and accommodated itself to the loss of the subcutaneous fat. It was smooth, soft, and exhibited a prolonged Sergeant's line. *There was no pigmentation.* Although every conceivable precaution was taken, bed-sores could not be prevented. No matter in what position the patient was placed, the skin over a bony prominence became gangrenous. His blood pressure was 154 systolic and 88 diastolic. Chemical examination of the blood plasma revealed the non-protein nitrogen to have risen to 61 mg. per

cent. The blood was dark red and viscid. The similarity between the patient's clinical picture and the state of chronic adrenal insufficiency in the experimental animal was noted.

On January 18, he had a chill and his temperature rose to 105° F. Signs of a bronchopneumonia appeared. He became comatose, his face assumed a grayish, pinched, mask-like expression and he slowly sank until his death on January 23. His temperature was subnormal terminally.

Autopsy. The body is markedly emaciated, weighing 70 pounds. There is a large decubitus ulcer over the sacrum measuring 6 cm. in diameter and smaller ones over the dorsal surfaces of the elbows and both ilia. *The subcutaneous fat is completely absent.*

Both pleural cavities are free of fluid. A few, easily separated, fibrous adhesions bind the left upper lobe to the thoracic wall. Interlobar adhesions are present between the right upper and middle lobes. The right lung weighs 315 gm. and the left 290 gm. The surfaces of both lungs are bluish in color, mottled with black. On section, they are red, smooth and moist. A few dark red, raised, granular, airless patches are present in both lower lobes.

The pericardial cavity is normal and contains about 10 cc. of clear, yellow fluid. The heart is markedly atrophic, weighing 160 gm., is brown in color and the epicardial fat is entirely absent. The coronary vessels are tortuous and surrounded by gelatinous tissue. The right ventricle and auricle are slightly dilated. The aortic, mitral, tricuspid and pulmonary leaflets are normal. The aorta exhibits a few atheromatous and calcified plaques in its ascending and thoracic portions. The coronary arteries are patent throughout.

There are moderately dense adhesions between the diaphragm and the anterior surfaces of both lobes of the liver and between the gall bladder and transverse colon. *There is complete absence of intra-abdominal fat—omental, mesenteric and perirenal.*

The liver is small, dark brown in color and cuts with slightly increased resistance. It weighs 850 gm. The central veins are engorged and the parenchyma has a yellowish-brown, homogeneous appearance.

The spleen is small, soft, covered by dense adhesions, and weighs 70 gm. The capsule is thickened. On section, the pulp is semi-diffuent and light red in color. The fibrous stroma is increased.

The stomach is small, contains some bile stained mucus and the mucosa exhibits irregular areas of congestion and hemorrhage.

The intestines show no gross abnormalities.

The pancreas is small and atrophic. The splenic artery is tortuous and sclerotic.

Both kidneys are small, each weighing 95 gm. The capsules strip with moderate ease leaving a very finely granular surface. On section, the cortex is slightly narrowed, and the markings are rather indistinct. The blood-vessels are prominent. There is no pelvic fat.

The adrenals appear enlarged in proportion to the marked atrophy of the other organs. The right adrenal weighs 9.2 gm. and the left 8.7 gm. No abnormalities are visible on the surface, and the suprarenal vessels are grossly normal. On section, the right adrenal exhibits a gray, grumous mass about 1 cm. in diameter which occupies the region of the medulla and the inner layer of the cortex. The normal lipid of the remaining portion of the cortex is replaced by grayish, homogeneous tissue. The left adrenal is similar in appearance to the right, except that the cheesy area is much smaller than that in the right adrenal and portions of the medulla are discernible.

The urinary bladder is small and contracted. The prostate is small, soft and grossly negative. The testicles are atrophic.

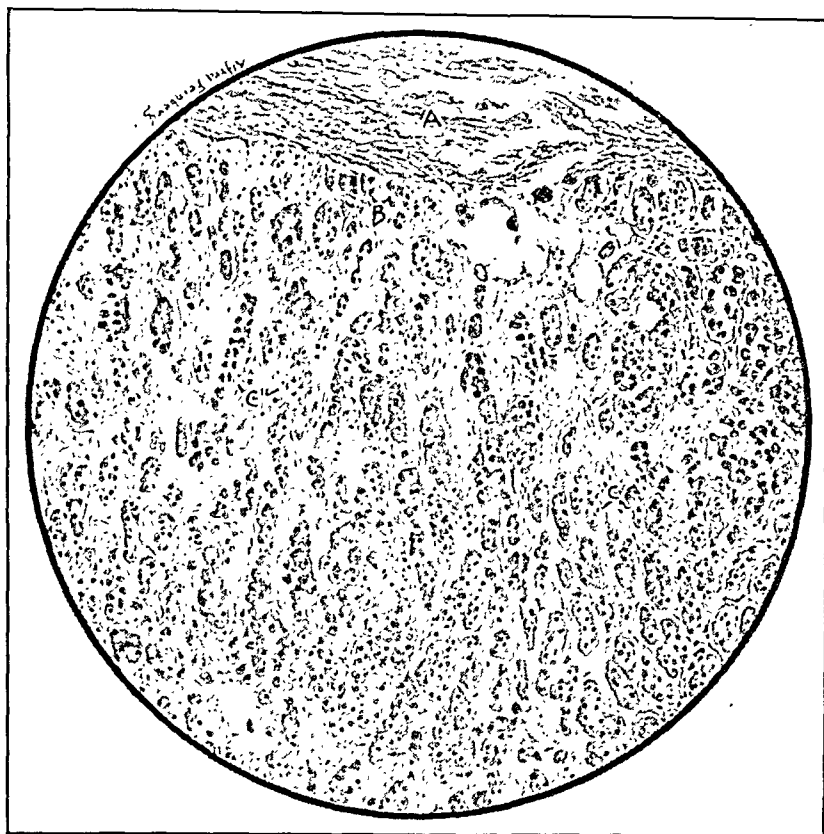


FIG. 1.—Section of right adrenal cortex, showing *A*, capsule; *B*, islands of regenerating cells in the zona glomerulosa, and *C*, collections of degenerating cells in the zona fasciculata separated by apparently thickened reticulum and giving this portion of the cortex a gland-like appearance. $\times 80$.

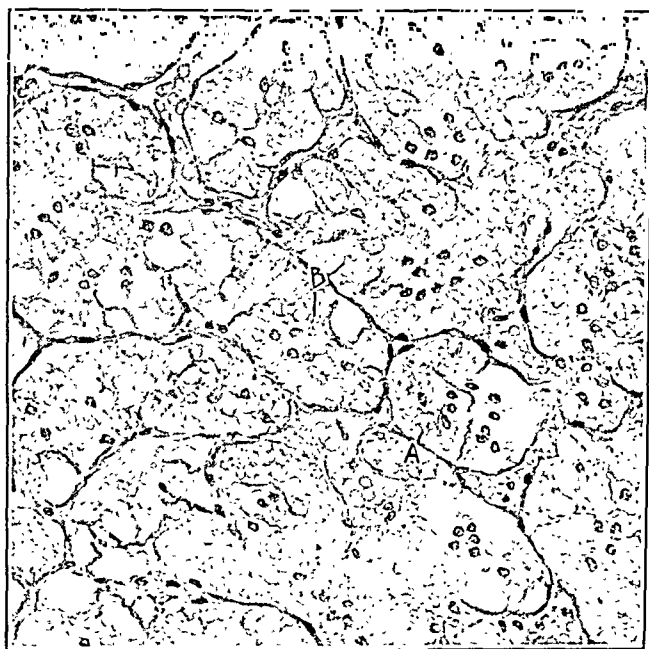


FIG. 2.—High magnification of zona fasciculata, showing *A*, enlarged weblike cells in which the nuclei are still well-preserved, and *B*, cells in which the degeneration is more advanced with fading out and disappearance of nuclei. $\times 400$.

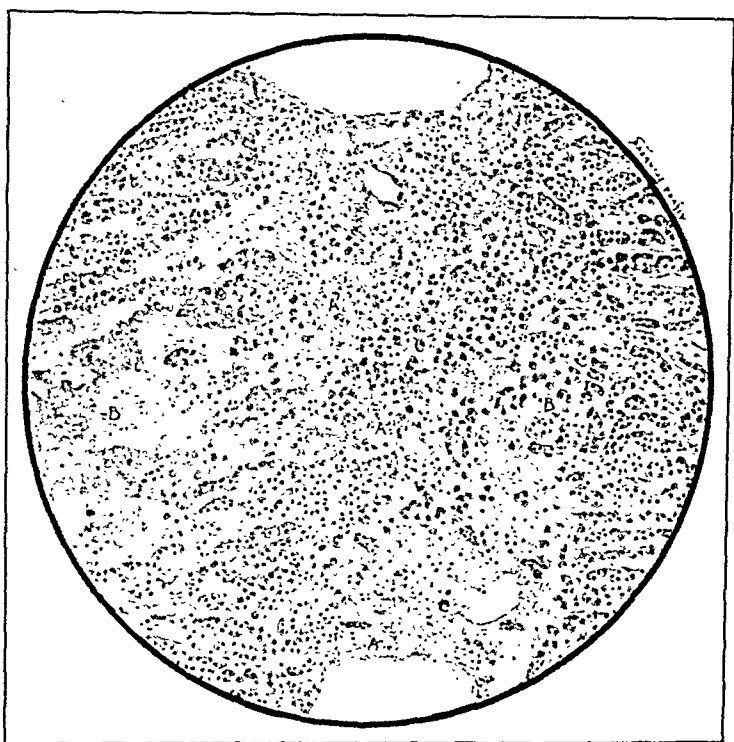


FIG. 3.—Section through central portion of right adrenal, showing *A*, deposits of extracellular hemosiderin pigment in zona reticulata and medulla; *B*, degenerating and necrotic cells of zona fasciculata, and *C*, absence of medullary tissue with only the reticulum still visible. $\times 80$.

The *thyroid* is small and somewhat firmer than normal. No *thymic* vestiges are found.

There is some increase in the subarachnoid and intraventricular fluid. The *meninges* are congested. The vessels of the circle of Willis show no sclerosis. The *brain* and *spinal cord* are grossly negative. The *pituitary gland* shows no gross abnormalities.

Microscopic examination confirms the marked atrophy of all the internal organs and the presence of a bronchopneumonia and an arteriosclerotic nephritis. Serial sections of the adrenals, however, reveal an advanced degenerative process (Fig. 1). The capsules are somewhat thickened. The architecture of the zona glomerulosa is irregularly distorted by what are apparently regenerating cells. The lipoid is present as finely granular particles in the degenerated areas, and is apparently reduced in amount. These are smaller, darker, polymorphic cells with homogeneous cytoplasm and do not exhibit the normal radial arrangement. The cells of the zona fasciculata are greatly enlarged and show marked vacuolar degeneration (Fig. 2). This degeneration can be traced through various stages to complete necrosis and eventual disappearance of the cells. The necrosis becomes more marked as the medulla is approached. Due to the absorption of large numbers of these cells, groups of enlarged, vacuolated cells are separated by apparently thickened reticulum, giving these portions of the cortex a gland-like appearance. In the right adrenal, intact medullary tissue cannot be found. In large areas it is completely necrotic, while in others only the reticulum is visible. Well-preserved areas of medullary tissue, however, are to be seen in the left adrenal. Marked hyperemia and numerous diffuse capillary and small venous thromboses are present. Especially in the zona reticulata and medulla are found many small hemorrhages and large amounts of hemosiderin pigment, mostly extracellular (Fig. 3). Focal collections of round cells are scanty. A moderate edema of the interstitial tissue is also present.

Anatomical Diagnosis. Cachexia with complete loss of adipose tissue and atrophy of the internal organs; decubitus ulcers over sacrum, elbows and ilia; chronic adhesive pleuritis; bronchopneumonia; dilatation of right heart; chronic perihepatitis, pericholecystitis and perisplenitis; congestion of liver; acute splenitis; arteriosclerotic nephritis; degeneration of adrenal glands.

Discussion. Unquestionably, on admission, our case was one of malnutritional edema. The history of inanition, the absence of other etiologic factors in the causation of edema both clinically and at autopsy and the spectacular response to a high caloric, vitamin B-rich diet admit of no other interpretation. This syndrome, moreover, has become so well known since the hunger blockade of the Great War and the post-war famines, that it needs no further comment here.

The puzzling feature of our case is the fact that in spite of the continuation of his diet and for no reason that could be demonstrated by clinical and laboratory examinations, the patient, in the second half of his illness, suddenly began the progressive deterioration previously described. The outstanding features were *the complete loss of body fat and an advanced degenerative lesion of both adrenals* with necrosis, regeneration, hemorrhages and capillary and venous thromboses.

Although this galaxy of symptoms is strongly reminiscent of

Addison's disease, the large number of atypical features present make this diagnosis untenable. While either the absence of pigmentation, gastro-intestinal disturbances, low blood pressure or practically complete destruction of the adrenal cortices can occasionally be present as individual aberrations from the typical syndrome, their combined absence in a single case militates strongly against such an assumption. *An additional differential point is the complete absence of body fat.* That loss of weight, often quite pronounced, occurs in the vast majority of cases of Addison's disease is well known. However, it never leads to marked cachexia, unless influenced by some such underlying disease as cancer. In most cases, it is moderate in degree and a definite adipose layer is present in the abdominal wall and in the abdomen.¹

There are two other diseases, pituitary cachexia and multiple endocrine gland sclerosis, which bear some resemblance to the case under discussion. Both, however, run an exquisitely chronic course. In the former, the emaciation is accompanied by wrinkling of the skin, falling out of the hair and teeth and at autopsy, a lesion of the pituitary gland is demonstrable. In the latter, there is grafted on the pituitary cachexia, symptoms of both myxedema and adrenal insufficiency.

The condition, we believe, forcibly suggests the state of chronic adrenal insufficiency in animals produced by bilateral suprarenal-ectomy described by Marine and Baumann² and by Jaffe.³ Jaffe summarizes the symptoms as follows: progressive emaciation with marked or complete loss of body fat, asthenia and liability to snuffles and skin infections. *The most striking phenomenon is the disappearance of the fat, which may be complete in animals with insufficiency of long standing.*

The effect of inanition and the various vitamin deficiencies on the adrenal glands has long been a matter of great interest. Jackson,⁴ who has exhaustively reviewed and analyzed the literature up to 1923, made the following digest: In the human adult during total inanition there is an increase in the size of the adrenals in most cases. In animals, it is usually very marked. Notable enlargement also occurs in partial inanition, especially in malnutritional edema. The enlargement appears to be due in some cases to an hypertrophy of the cortex, in others of the medulla or of both. There is a congestion of the bloodvessels and sometimes hemorrhage. A variable degree of cell atrophy is present. The behavior of the lipid and pigment is variable, although the latter is frequently increased. In the medulla, the changes are less marked and less frequent than in the cortex.

A review of recent experimental work reveals that it is still a moot question both as to whether these changes are due to inanition or B-avitaminosis and as to what portion of the gland is affected. Some investigators attribute them specifically to a lack of vitamin B.⁵

others to both inanition and vitamin B deficiency,⁶ while still others claim that the hypertrophy is less marked in inanition.⁷ The difficulty of differentiating between the effects of inanition and vitamin B deficiency is still further complicated by the apparent multiplicity of the latter. The hypertrophy in vitamin-B deficient pigeons, according to Marrian *et al.*,⁸ is due mainly to B¹, but B² is a contributory factor. Findlay⁹ found that it occurred in rats lacking either B¹ or B². The confusion is just as marked with regard to the location of the hypertrophy. Recently, it has been hypothesized that with starvation, there is an hypertrophy of the medulla, and with vitamin B deficiency, of the cortex.¹⁰ The microscopic changes have received scant investigation.

It is obvious that the adrenal changes described, both in the human adult and the experimental animal, do not represent a true hypertrophy. The increase in weight of the adrenals is due to congestion, hemorrhage, and regeneration. Marrian¹⁰ found a 19 per cent increase in the water content of the adrenals of pigeons on vitamin B-deficient diets and a 44 per cent increase after starvation.

It is conceivable that the degenerative lesions in the cortex, medulla or both could occasionally outweigh these factors and produce normal sized or even shrunken adrenals, thus accounting for some of the discordant results.

The alterations in structure must manifestly affect the functions of the gland, though experimental and clinical data appertaining to this question are meager. McCarrison¹¹ has reported changes in the adrenalin content of the suprarenals of animals fed on a variety of deficient diets. Peiser¹² compared the adrenalin content of the suprarenals secured at autopsy from subjects dying during the hunger blockade with those before the war, and found it to be two-thirds of the pre-war amount. Sehrt¹³ has called attention to the ineffectiveness of the adrenalin extracted from animal adrenals during the blockade.

In human malnutrition, the significance of the changes in size, structure and function of the adrenals and the clinical symptoms they produce, if any, are unknown. We have been able to find but two observations bearing on this question. In reviewing his extensive experience with malnutritional edema, Tallqvist¹⁴ states that the symptoms indicate both thyroid and adrenal insufficiency. Enright¹⁵ has reported 54 cases of malnutritional edema in which the outstanding features at autopsy were a complete loss of body fat and shrunken adrenals. These cases closely approximate the one under discussion, but, unfortunately, all of them were associated with some other disease, usually pellagra. He considers the clinical picture to be due to a combination of debilitating disease and food deficiency operating to produce an adrenal insufficiency.

The uncomplicated chain of events in our patient, in conjunction with the findings at autopsy, establishes, we believe, not only a con-

nection between malnutritional edema and adrenal degeneration but a clinical syndrome of chronic adrenal insufficiency which closely resembles that state in the experimental animal. The conception of a relationship between malnutrition and adrenal changes is supported by a wealth of clinical and experimental observations and, moreover, is not unique; as another nutritional disturbance, rickets, is frequently associated with lesions of the parathyroid glands. In fact, Wells¹⁶ has suggested a dietary imbalance as a possible factor in idiopathic adrenal atrophy. Exact proof, however, of the causal relationship between the morphologic findings in the adrenals and the clinical symptoms exhibited by the patient must await a quantitative measure of adrenal function and a reliable substitution therapy.

Summary. 1. A case of malnutritional edema is reported which exhibited an unusual clinical syndrome and a degenerative lesion of the adrenals at autopsy.

2. The outstanding clinical features were extreme emaciation with complete loss of body fat, asthenia, anorexia, polyneuritis, trophic ulcers and absence of pigmentation and hypotension.

3. The similarity between the syndrome and the state of chronic adrenal insufficiency in animals produced by bilateral suprarenalec-tomy is pointed out.

4. The literature on the effect of total and partial inanition and the various vitamin deficiencies on the adrenal glands in both animals and man is reviewed.

5. It is suggested that this clinical syndrome, hitherto unde-scribed, is one of chronic adrenal insufficiency due to the adrenal degeneration occasioned by malnutrition.

We have recently observed a case of malnutritional edema in an Italian male, aged 53 years, who presented the same syndrome as that described above, with certain exceptions. The edema was not as pronounced. The course was more rapid, and the loss of subcutaneous fat, though extreme, had not reached a total disappearance. At autopsy, the right adrenal was completely absent except for a few shreds of tissue, which on microscopic examination showed the typical changes described in idiopathic adrenal atrophy. The left adrenal was markedly hypertrophied, weighing 12.8 gm., and microscopic examination showed a degenerative process similar to but much less advanced than that in the first case.

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HYPERMOTILITY OF THE GASTRO-INTESTINAL TRACT IN HYPERTHYROIDISM.

A STUDY OF 42 CASES.

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HYPERMOTILITY of the gastro-intestinal tract in hyperthyroidism has received little or no mention in the literature, although this is a prominent symptom in many patients with thyroid disease. Hence, a series of 42 patients with thyroid disease were studied at the Cleveland Clinic. These patients were examined before operation and again 7 to 10 days after thyroidectomy. The studies were made with the regular barium meal used for investigation of the gastro-intestinal tract. Fluoroscopic examinations were made at the time of ingestion of the meal, and 3 hours later roentgenograms were made to locate the head of the barium meal.

Hurst¹ suggested an average rate or time table for the "head" of the ingested meal as follows: cecum, 4 hours; hepatic flexure, 6 hours; splenic flexure, 9 hours; pelvic colon (sigmoid), 12 hours.

Béclère and Meriel,² and others, have stated that after $\frac{1}{2}$ hour the opaque meal may be seen on the left and in the midabdomen. After 2 hours it usually is found in the middle and lower abdomen. After 4 hours it occupies only a portion of the ileum and is already manifest in the cecum. At 6 hours only a little remains in the terminal ileum. At the end of 8 hours the small bowel is completely empty. The investigations of Hurst showed that after a barium test meal the shadow of the cecum began to appear $4\frac{3}{8}$ hours after ingestion. He computed the rate at which the intestinal contents travel as about 2.5 cm. per minute. Carman³ stated that at the end of 6 hours, when the stomach is empty and the head of the meal is found between the cecum and the hepatic flexure,

the gastro-intestinal motility is considered to be normal. This is true if there is no deviation from the normal of other factors, such as acidity, peristalsis, tonus and pyloric function. Further, he added that a degree of hypermotility, as evidenced by advancement of the meal beyond the hepatic flexure and by the rapid discharge of the second meal through the pylorus, not rarely has a physiologic explanation, such as, for example, the presence of a hypertonic steer-horn stomach. But he felt that roentgenologic evidence of marked hypermotility should stimulate a search for possible causes. In the presence of a decided hypermotility Carman stated that duodenal ulcer, gastric carcinoma, anacidity and diarrhea should be considered as possible causes. He made no mention of hyperthyroidism.

Examination of patients with hypothyroidism by Warfield⁴ showed ptosis of the stomach with retention of the barium meal in the descending colon and sigmoid for from 56 to 72 hours.

Wohl⁵ recently reported observation in patients with hypothyroidism who showed marked hypomotility in the gastro-intestinal tract. He summarized the part played by the autonomic nervous system as follows: Vagotonia supposedly is associated with hypermotility, increased peristalsis and increased gastric secretion. The nerves of the sympathetic group produce the opposite or inhibiting effect on the gastro-intestinal canal and are presumed to be responsible for delayed emptying of the stomach, the diminished gastric secretions and also diminished gastric peristalsis. Eppinger and Hess⁶ spoke of a balance between the vagus and sympathetic nervous systems which they believed was maintained by the effect of the secretions of the ductless glands on the whole autonomic nervous system.

The occurrence of hypermotility of the colon in 10 per cent and of stasis of the colon in 30 per cent of a series of cases with achlorhydria reported by Hitzrot⁷ leaves some doubt as to Carman's suggestion regarding the part played by anacidity or achlorhydria in the production of gastric hypermotility.

The clinical significance of a study of gastro-intestinal hypermotility associated with thyroid disease is apparent when one considers the significance of digestion and absorption in the intestinal canal. Howell⁸ pointed out that food undergoes its most profound digestive changes in the intestines, and that it is here also that the products of digestion are mainly absorbed. Intestinal digestion begins in the duodenum and is largely completed by the time that the food arrives at the ileocecal valve. Thus, in extreme hypermotility of the intestine, there is probably very great disturbance of the functions of digestion and absorption. An analysis of the cases studied is shown in Table 1.

If one uses Hurst's standard for the estimation of hypermotility,

it would be safe in stating that if the head of the meal in 3 hours is beyond the cecum, there is hypermotility of the gastro-intestinal canal. In analyzing this series of cases it was found that by the above criteria, 39 cases (92.8 per cent) manifested hypermotility of the gastro-intestinal tract before operation. In 2 cases (4.7 per cent) the head of the barium was in the cecum within 3 hours. In only 1 case (2.3 per cent) of the series was the barium in the small bowel, showing a normal motility at the end of 3 hours.

TABLE 1.

No.	Age.	Sex.	Wt. loss, lbs.	Head of barium before operation.	Head of barium after operation.	Bowel habits.	Operation.
1	21	F	24	Ascending colon	Hepatic flexure	Constipation	Posterior ligation.
2	50	F	20	Descending colon	Small bowel	Constipation	Thyroidectomy.
3	21	M	20	Rectum	Cecum	Irregular	Thyroidectomy.
4	33	F	39	Rectum	Splenic flexure	Diarrhea occ.	Thyroidectomy.
5	44	F	25	Small bowel	Cecum	Regular	Thyroidectomy.
6	57	F	28	Splenic flexure	Cecum	Constipation	Lobectomy.
7	29	F	25	Rectum	Cecum	Overactive	Thyroidectomy.
8	29	M	8	Splenic flexure	Cecum	Regular	Thyroidectomy.
9	35	F	25	Hepatic flexure	Small bowel	Regular	Thyroidectomy.
10	37	F	25	Splenic flexure	Ascending colon	Regular	Thyroidectomy.
11	41	F	58	Splenic flexure	Sigmoid	Constipation	Thyroidectomy (recurrent).
12	24	F	9½	Rectum	Small bowel	Regular	Thyroidectomy.
13	45	M	10	Transverse colon	Transverse colon	Normal	Thyroidectomy.
14	34	F	30	Transverse colon	Cecum	Constipation	Thyroidectomy.
15	25	F	30	Cecum	Small bowel	Constipation	Lobectomy.
16	35	M	13	Sigmoid colon	Descending colon	Constipation	Thyroidectomy.
17	31	M	38	Transverse colon	Rectum	Regular	Ligation.
18	40	F	40	Rectum	Rectum	Regular	Thyroidectomy.
19	21	F	6	Rectum	Transverse colon	Regular	Thyroidectomy.
20	12	F	0	Rectum	Rectum	Regular	Thyroidectomy.
21	50	F	19	Rectum	Hepatic flexure	Regular	Thyroidectomy.
22	21	F	0	Sigmoid flexure	Cecum	Regular	Thyroidectomy.
23	25	F	5	Splenic flexure	Descending colon	Constipation	Thyroidectomy.
24	38	F	20	Rectum	Hepatic flexure	Overactive	Thyroidectomy.
25	44	M	60	Rectum	Rectum	Ulc. colitis	Lobectomy.
26	26	F	40	Hepatic flexure	Cecum	Constipation	Thyroidectomy.
27	44	F	20	Sigmoid	Transverse colon	Diarrhea occ.	Thyroidectomy.
28	52	F	21	Cecum	Hepatic flexure	Constipation	Thyroidectomy.
29	41	F	0	Rectum	Splenic flexure	Constipation	Thyroidectomy.
30	54	F	46	Rectum	Ascending colon	Regular	Lobectomy.
31	51	F	12	Splenic flexure	Cecum	Constipation	Thyroidectomy (recurrent).
32	46	F	25	Hepatic flexure	Cecum	Regular	Thyroidectomy.
33	52	F	12	Hepatic flexure	Cecum	Regular	Thyroidectomy.
34	50	F	4	Splenic flexure	Transverse colon	Regular	Thyroidectomy.
35	18	F	19	Rectum	Hepatic flexure	Regular	Thyroidectomy.
36	34	F	12	Sigmoid colon	Hepatic flexure	Regular	Thyroidectomy.
37	23	F	0	Splenic flexure	Cecum	Diarrhea	Thyroidectomy.
38	41	F	42	Splenic flexure	Cecum	Constipation	Thyroidectomy.
39	43	M	4	Sigmoid	Cecum	Regular	Thyroidectomy.
40	27	F	0	Sigmoid	Ascending colon	Regular	Thyroidectomy.
41	46	F	29	Splenic flexure	Ascending colon	Regular	Thyroidectomy.
42	22	F	25	Rectum	Splenic flexure	Regular	Thyroidectomy.

The analysis of the motility after operation is rather difficult to present because, by percentage statistics the true significance of the results obtained is not elicited. Figure 1 illustrates the position of the head of the meal in the 42 cases both before and after operation on the thyroid gland. The solid dot represents the position pre-operatively and the solid triangles the position postoperatively.

It shows that in most instances before operation the site of the barium meal was beyond the mid-colon and that after operation in most cases it was located to the right of the mid-colon.

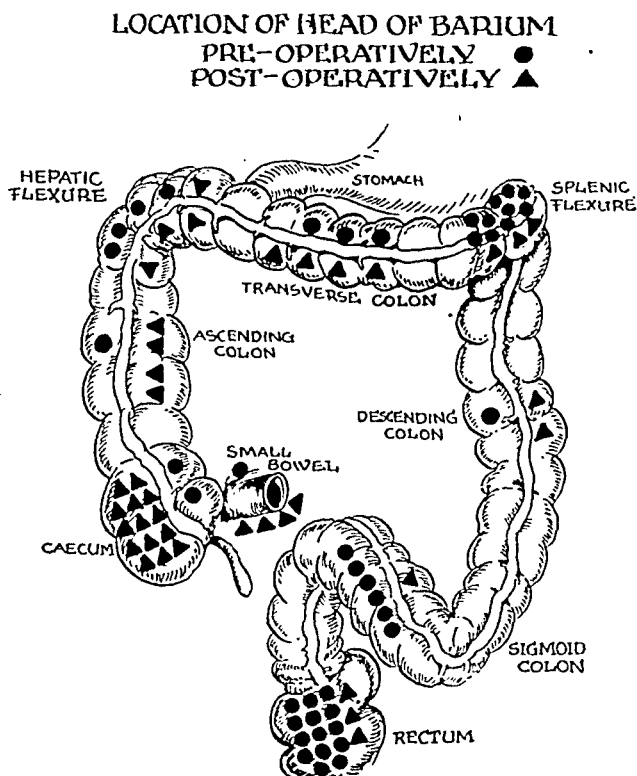


FIG. 1.—Schematic drawing, showing location of head of barium meal before and after thyroid operations.

Table 2 indicates the changes which took place in the location of the barium meal after operation.

TABLE 2.—CHANGES IN THE LOCATION OF THE BARIUM MEAL AFTER THYROIDECTOMY.

	Motility.		
	Unchanged.	Increased.	Decreased.
Head of barium:			
Rectum	3	0	11
Sigmoid	0	1	6
Descending colon	0	0	1
Splenic flexure	0	1	8
Transverse colon	1	1	1
Hepatic flexure	0	0	4
Ascending colon	0	1	0
Cecum	0	1	0
Small bowel	0	1	0
	—	—	—
Total cases	4	6	32
Per cent	9.54	14.27	76.19

FIG. 2a

FIG. 2b

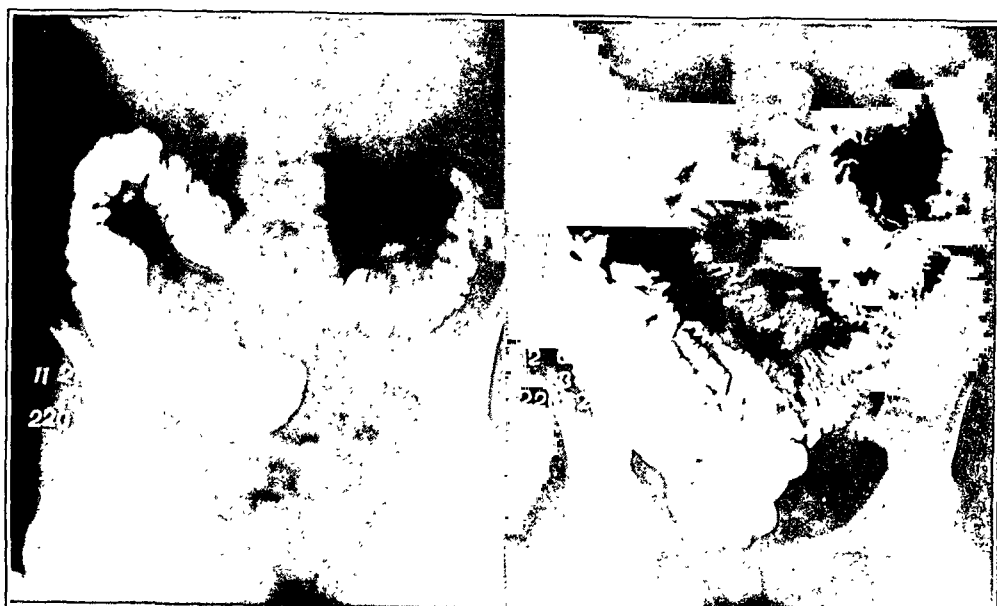


FIG. 3a

FIG. 3b

FIG. 2.—(a) Before operation. (b) Nine days after thyroidectomy.

FIG. 3.—(a) Roentgenogram of colon before operation. (b) Roentgenogram of colon 5 days after thyroidectomy.

FIG. 4a

FIG. 4b



FIG. 5a

FIG. 5b

FIG. 4.—(a) Roentgenogram of colon before operation. (b) Roentgenogram of colon 9 days after thyroidectomy.

FIG. 5.—(a) Roentgenogram of colon before operation. (b) Roentgenogram of colon 6 days after thyroidectomy.

The striking point in this analysis is the apparent change in the gastric motility which follows the clinical control of the hyperthyroidism. It would not be too much to say that these results show that there was some general systemic alteration following the removal of the thyroid.

The fact that there were 6 cases in which the intestinal motility was increased following operation is very interesting. One of these patients was subjected to bilateral ligation of the superior thyroid arteries, from which operation could not be expected such rapid clinical improvement as that following removal of the gland. Another of these patients in whom gastro-intestinal motility increased following operation was a child, aged 12 years, who was moderately active. In the group of cases in which there was no change after operation, 1 patient had chronic ulcerative colitis which persisted and probably had much to do with the hypermotility. The others offered no clinical evidence after the operation on the thyroid to account for persistence of an increased rate of movement in the gastro-intestinal tract.

The group in which there was a definite decrease in the motility following operation on the thyroid included 32 cases (76.19 per cent). This figure becomes even more significant when the degree of retardation in the hypermotility is analyzed. Table 3 shows the amount of retardation of movement calculated by comparison with the location of the barium meal before operation.

TABLE 3.—AMOUNT OF CHANGE IN GASTRO-INTESTINAL MOTILITY FOLLOWING OPERATION ON THE THYROID GLAND.

	Pre-operative location.	Slowed.	Per cent slowed.
Rectum	14	11	78 50
Sigmoid	6	6	100 00
Descending colon	1	1	100 00
Splenic flexure	10	8	80 00
Transverse colon	3	1	33.33
Hepatic flexure	4	4	100.00
Ascending colon	1	0	
Cecum	2	0	
Small bowel	1	0	

The following illustrations are from roentgenograms made on the same patients 3 hours after ingestion of the barium meal both before and after thyroid operation (Figs. 2 and 3).

In analyzing the bowel habits of the patients in this series it was found that 13 patients (30.9 per cent) were constipated, 6 patients (14.2 per cent) had diarrhea and 23 patients (54.8 per cent) had regular bowel movements.

In the cases with diarrhea 1 patient had chronic ulcerative colitis which accounted entirely for this finding. The others, however, were patients with uncomplicated hyperthyroidism.

It was possible in 12 cases to study the gastric secretions by means of the Rehfuess fractional test meal. In these 12 cases all but 2 patients showed a very marked hypermotility of the gastro-intestinal canal. Free hydrochloric acid and total acid was found to be low in 5 cases (41.6 per cent). Free hydrochloric acid was absent in 6 cases (50 per cent), and there was normal free hydrochloric acid in 1 case (8.4 per cent).

The most important clinical finding that this problem has educed is the association of the finding of low serum protein in cases of hyperthyroidism. This will be reported in a later paper. But it seems apparent that in the short time required for passage of the barium through the digestive canal, as demonstrated by these observations, it would be rather difficult for a patient with severe hyperthyroidism having marked hypermotility of the gastro-intestinal tract to assimilate the ingested foods completely. The fact that the barium meal reaches the rectum within 3 hours indicates that food is retained for a very short period in the small intestine, the area of greatest absorption. The exact amount of decrease in the absorption of foods is a problem to be worked out. But certainly in view of the rapid passage of ingested material through the bowel one can only conjecture that there would be decreased assimilation brought about by the hypermotility of the gastro-intestinal canal.

Summary.—1. The study of a series of 42 patients with hyperthyroidism showed that hypermotility of the gastro-intestinal canal occurs in this condition but that the degree of hypermotility is not an index to the severity of the disease.

2. Hypermotility of the gastro-intestinal tract was decreased, usually markedly, after removal of the thyroid in 76 per cent of the cases studied.

3. Hypermotility and anacidity occurred concomitantly in 12 cases of hyperthyroidism in this series.

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THE CORROBORATIVE VALUE OF AN IMPROVED GASTRO-DUODENAL BRAID IN THE DIAGNOSIS OF PEPTIC ULCER.

A COMPARATIVE STUDY OF ONE HUNDRED CASES.

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THE diagnosis of some diseases of the gastro-intestinal tract is at times so baffling that it taxes the ingenuity of the most experienced. No individual test, no matter how trivial, can be considered superfluous in corroborating the more important data at hand, and so aid in arriving at a final diagnosis.

For instance, in the diagnosis of peptic ulcer a good history is highly suggestive, the roentgenologic evidence is usually conclusive. Yet certain types of cases are encountered where either the history is atypical, the roentgenologic findings are insufficient and the laboratory data inconclusive. There is still another group of patients which displays a typical duodenal ulcer syndrome and proves to be normal roentgenologically, insofar as our criteria for diagnosing peptic ulcer is concerned. Such cases I have reported in a recent communication,¹ where I suggested that these cases be designated under the name of "subacute recurrent duodenitis." In this condition the history strongly suggests duodenal ulcer. Upon Roentgen ray examination, however, no evidence of ulcer can be found. The duodenal bulb appears hazy, displays signs of marked irritability, with rapid emptying. In view of such evidence one is reluctant in venturing a positive diagnosis of ulcer, and is compelled to resort to further search.

Other conditions frequently offering difficulties in diagnosis are periduodenal adhesions, either caused by disease in an adjacent organ, such as the gall bladder, or distortion of the duodenal bulb, as a result of scarring produced by a healed ulcer. Determining whether an ulcer is active or not, in the absence of definite symptoms, is also frequently a difficult point to decide by means of Roentgen ray evidence alone.

The purpose of this paper is to report on the diagnostic value of a gastroduodenal braid, which was first described by Cash² in 1923. This braid is actually a modification of the silk string and duodenal bucket described by Einhorn³ in 1909. It has very distinct advantages over the Einhorn string, and these I will soon mention. The Cash braid (Fig. 1) consists of a proximal and a distal portion. The proximal portion is loosely knitted, tubular silk braid, $\frac{1}{2}$ inch in diameter, about 13 inches in length, and is white, flexible and

compressible. The distal portion which is attached to the proximal, is a twisted No. 15 silk string 17 inches long, having a knot 4 inches from its distal end, indicating the lip mark. The entire length of the braid available for swallowing is about 26 inches.

The braid is swallowed before retiring, several hours after the evening meal, and is allowed to remain over night. The patient is

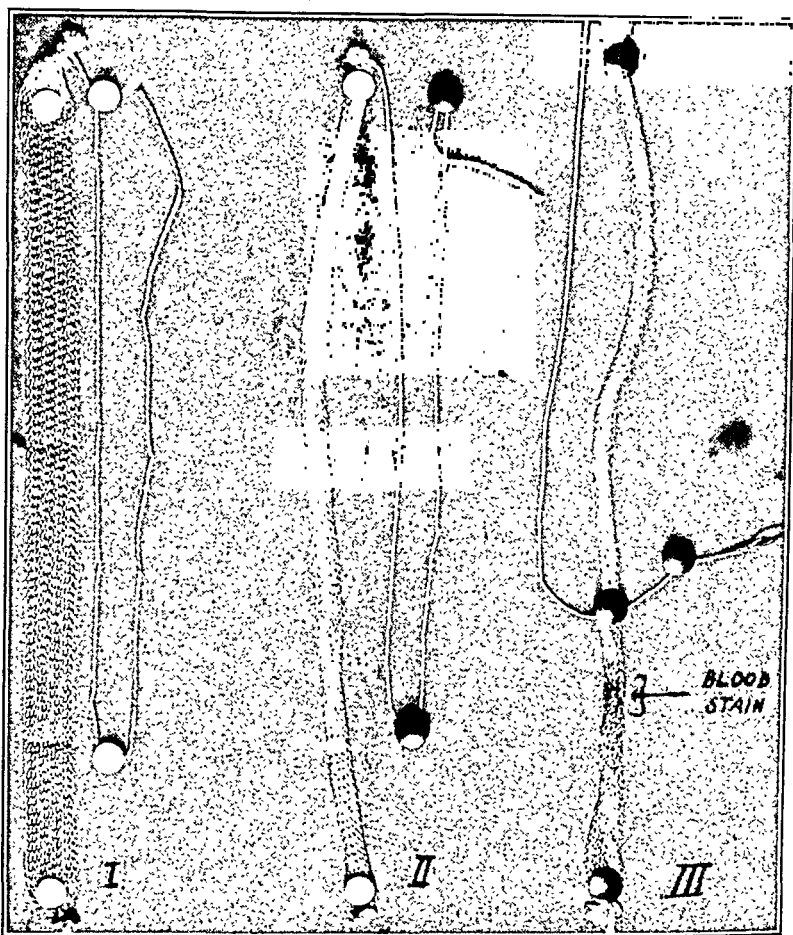


FIG. 1.—Showing the modified gastroduodenal braid. *I*, appearance of the braid before it is swallowed; *II*, appearance of the braid after remaining in the gastroduodenal tract overnight; *III*, demonstration of a localized blood stain in an ulcer case.

instructed not to partake of any food or beverage which may color the braid. The distal 4 inches of the braid are affixed to the cheek by a piece of adhesive plaster to prevent swallowing of entire braid during sleep.

The advantages of this braid are quite obvious. It offers a large surface for contact with the ulcer area, producing usually a

very definite blood stain. Because of its compressibility the compression or narrowing produced on the braid by the pyloric sphincter can be easily made out, thus localizing this part of the stomach and thereby the lesion, whether gastric or duodenal. Bile stains can also be readily detected, and are at times invaluable evidence of a chronic duodenal obstruction or duodenal dilatation, as our observations compared with roentgenologic findings have definitely shown in many cases. The size and texture of this braid is such that prevents abrading of the gastroduodenal mucosa, as frequently may be the case when using an ordinary string, in an irritable stomach with a sensitive, hyperemic mucosa.

One learns by experience that only an isolated localized stain is pathognomonic of ulcer. Diffuse staining of the braid is usually caused by bleeding from the gums or throat; rarely by the braid coming in contact with a hyperemic mucosa. In gastric malignancies the stain is frequently diffuse, though rather distinctly deep in color. Food may at times color the braid, but one can easily distinguish the type of stain.

This study comprises a series of 100 cases (95 hospital and 5 private) on whom complete roentgenologic studies of the gastrointestinal tract have been made, always preceded by the necessary examinations and administration of the braid. In some suspicious cases 2 or 3 braids had to be administered in order to arrive at a definite conclusion. The braid observations have been checked with the roentgenologic reports with reference to two findings: (1) Blood stain, indicating peptic ulcer, and (2) a deeply colored bile stain which we have learned to denote duodenal dilatation or chronic duodenal obstruction. (See Tables 1 and 2.)

TABLE 1.—RELATION OF BRAID TO ROENTGEN RAY FINDINGS AND HISTORY IN ULCER DIAGNOSIS.

	Braid stain.	Ulcer by Roentgen ray.	History.	Cases.
A	Negative	Negative	Nonsuggestive	45
B	Negative	Negative	Suggestive	10
C	Positive	Positive	Nonsuggestive	9
D	Positive	Positive	Suggestive	15
E	Positive	Negative	Nonsuggestive	11
F	Positive	Negative	Suggestive	2
G	Negative	Positive	Nonsuggestive	3
H*	Negative	Positive	Suggestive	5

* 2 of these found positive at operation.

TABLE 2.—RELATION OF BRAID TO ROENTGEN RAY FINDINGS IN DIAGNOSIS OF DUODENAL DILATATION.

	Bile stain.	Duodenal dilatation.	Cases.
A	Present	Found	32
B	Present	None found	4
C	Absent	Found	23
D	Absent	None found	41

Results and Comment. As will be seen from Table 1, of the 100 cases studied, 32 were diagnosed roentgenologically as peptic ulcer (24 duodenal and 8 gastric). Five additional cases were diagnosed by Roentgen ray as doubtful cases of ulcer, and the braid was negative for blood stain in each instance. These cases were not included in our ulcer group, although they lend additional evidence to the corroborative value of the braid in the diagnosis of peptic ulcer.

Ten of the 100 cases came to operation, 3 of which were diagnosed as ulcers by Roentgen ray and by the braid test and corroborated at operation. In 2 cases the Roentgen ray evidence seemed to favor a diagnosis of duodenal ulcer, the braid showed no evidence of blood stain, and no ulcers were found at operation. The remaining 5 cases were miscellaneous surgical entities, our pre-operative diagnoses being corroborated at operation.

Of the 32 cases diagnosed roentgenologically as ulcer, 24 (75 per cent) showed a definite, localized blood stain on the braid. Of the remaining 8 cases which failed to show braid evidence of ulcer as compared with Roentgen ray diagnosis, 2 cases subsequently were proven to be ulcers at operation. We are thoroughly convinced that although the above incidence of blood positive braids may appear high, yet similar results may be obtained in any group of suspicious ulcer cases, providing thorough search for blood stain is made, and the braid test repeated two or three times, if such procedure is warranted.

Ulcer History in Comparison to Blood Stain. It was interesting in this study to compare the history, in the group of ulcer cases with the braid and Roentgen ray findings, in view of the fact that the history is so typical in a good many ulcer patients. In Table 1 we find that of the 32 Roentgen ray positive cases, 20 (62.5 per cent) gave a suggestive ulcer history. Of the remaining 12 with a non-suggestive history, 9 cases (75 per cent) showed a positive blood stain on the braid, indicating a probable gastric or duodenal lesion. This again indicates the superiority of the braid evidence over the history. In 5 of the cases (15.6 per cent) the history and Roentgen ray findings were positive, although the braid showed no evidence of any blood stain. Comparing then the history with the braid findings, we obtained 62.5 per cent positive histories as against 75 per cent positive blood stained braids, in the entire group of ulcer cases.

Braid Evidence of Duodenal Dilatation. In 55 of our 100 cases, the Roentgen ray examination revealed some degree of dilatation of some portion of the duodenum—rather a high incidence. Of these, 32 (58.1 per cent) were diagnosed by the braid as having some form of duodenal stasis, as manifested by a deep, diffuse, golden, dark yellowish or greenish discoloration of the distal 2 or 3 inches of the braid. As before mentioned, we have come to recognize this finding as being indicative of a duodenal stasis in quite a large proportion

of cases. The doubtful cases of bile stained braids were not included in this group.

In 4 cases the braid showed a definite bile stain, although our roentgenologist was unable to confirm the findings of duodenal abnormality. In 23 patients the Roentgen ray showed evidence of duodenal dilatation, while the braid findings were negative. As to whether the findings of duodenal dilatation in our group of cases were responsible for symptoms, we are at present not prepared to say. Undoubtedly in a certain proportion of cases the symptomatology may have been attributed to some degree of duodenal stasis.

Summary and Conclusions. The results of a comparative study of the corroborative diagnostic value of the gastroduodenal braid are herein reported. The advantages of the braid over the Einhorn string are described.

In a series of 100 cases in which a complete roentgenologic study of the gastro-intestinal tract has been made, followed by the administration of the braid, the braid results have been checked with the Roentgen ray findings with reference to two signs: (1) A localized blood stain, indicating a probable peptic ulcer, and (2) a deeply colored bile stain, which we learned to recognize as a sign of a possible duodenal stasis. The diagnostic value of a suggestive ulcer history has also been compared with the braid and Roentgen ray findings.

Of 100 cases studied, 32 were diagnosed roentgenologically as peptic ulcer (24 duodenal and 8 gastric). Five of these came to operation. Of the entire group of ulcer cases, 75 per cent have shown a definite blood stain on the braid, indicating ulcer. In 2 cases the braid was positive for blood, the Roentgen ray findings were negative, and ulcer was found at operation, while in 2 other cases which came to operation, the braid was negative, the Roentgen ray findings were positive, and ulcer was found at operation.

Comparing the history with the braid findings in the same group of cases, we obtained in 62.5 per cent of the patients histories that were suggestive of peptic ulcer, as against 75 per cent positive blood stained braids.

In 55 of the 100 cases the Roentgen ray examination revealed some degree of duodenal dilatation. Of these, 32 (58.1 per cent) were diagnosed by the gastroduodenal braid.

The results of this study readily demonstrate the value of the gastroduodenal braid as an adjunct in the diagnosis of peptic ulcer.

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SHORT INTERVAL OBSERVATIONS ON THE BLOOD IN PERNICIOUS ANEMIA AFTER NON-PURIFIED LIVER EXTRACT INTRAVENOUSLY.*

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IN 1930 Gänsslen reported 100 cases of anemia treated successfully with intravenous liver extract therapy, of which more than 40 were pernicious anemia. Unfortunately he gave no description of the preparation injected. Schilling, using Gänsslen's extract, confirmed his results and reported a series of 10 more cases of pernicious anemia with adequate treatment. Others who have made effective intravenous liver extracts are Cohn, West and their respective collaborators, Castle and Taylor, and Aubertin and Voillemin.

As a remission can be produced *very promptly* by the injection of liver extract intravenously, it was decided to use this method to study the early changes in the blood with the onset of the reticulo-cyte response. This method has the advantage that the changes can be timed very carefully after the administration of a known amount of the substance, eliminating the uncertainties of absorption by the oral or intramuscular routes. The blood of the 2 cases reported here was observed at 4-hour intervals day and night for 11 days.

Material and Methods. The liver extract used in Patient 1 was prepared according to the method of Castle and Taylor.¹ Lilly's No. 343 was extracted with ether, dissolved in physiologic salt solution, boiled for 3 minutes, filtered and boiled for 2 more minutes. The dosage given was 0.1 gm. per kg. body weight, which in this patient amounted to 10 gm. of the liver extract. The total volume given was 80 cc.

The second patient was given an extract similar to the above. This patient received 6.5 gm. of Lilly's liver extract No. 343, in a 50 cc. aqueous solution.

* Presented before the Central Society for Clinical Research, November 20, 1931. See Abstract, J. Clin. Invest., 1932, 11, 860.

The injections were given very slowly, at the rate of approximately 4 cc. per minute. Blood pressure observations were made before and at frequent intervals after the injection, until the pressure became stabilized at the pre-treatment level.

The blood counts were made according to the usual methods, using U. S. Bureau of Standards certified pipettes and counting chambers. The hemoglobin was estimated by the Leitz-Sahli apparatus (14 gm. = 100 per cent). Complete counts were made twice daily, at 8 A.M. and 8 P.M., and Wright stained cover-glass films (brilliant cresyl blue and plain) at 4-hour intervals, day and night. During the period of observation the patients remained in bed. Each patient was given a routine house diet with no liver or kidney.

Case Histories. CASE 1.—Mr. P. P., aged 47 years (second relapse), had been diagnosed as having pernicious anemia in 1926, the outstanding features at that time being pallor, ease of fatigue, tiredness, dyspnea, numbness and tingling of extremities, nausea and vomiting, and increasing constipation. The patient had been on liver diet for 1½ years and then discontinued it. He felt well until 1 month previous to the present study, at which time he had a complete relapse. Physical examination revealed an adult male, extremely pale, icteric scleræ, atrophic tongue and pitting edema of the ankles. On admission the red blood cell count was 1,570,000 per c.mm., hemoglobin 41 per cent (Sahli) and white blood cell count 5800 per c.mm. Gastric analysis following the intramuscular injection of 1 mg. of histamin hydrochlorid showed no free hydrochloric acid. The patient received 10 gm. of Lilly's liver extract made up in solution with 80 cc. of 0.8 per cent sodium chlorid solution.

CASE 2.—Mr. J. S., aged 68 years (first relapse), felt comparatively well until 5 months previous to the present study. Since then he has noted a very poor appetite associated with numbness and tingling of the extremities, edema of the ankles, dyspnea, palpitation, dizziness, weakness, ease of fatigue and pallor. There was a loss of 15 pounds in weight. Physical examination revealed an adult male subacutely ill, lemon tint of the skin, mucous membranes pale, scleræ icteric, tongue papillæ atrophic, vibratory sense diminished over the bones of the left leg. No free hydrochloric acid was present in the gastric contents following histamin hydrochlorid injection. On admission the red blood cell count was 1,100,000 per c.mm., and hemoglobin 22 per cent (Sahli) and white blood cell count 4900 per c.mm. The patient was given 6.5 gm. of Lilly's liver extract No. 343, made up in a solution of 50 cc. of distilled water.

A definite response to the therapy as evidenced by an increase in the reticulocyte percentage was noted at the end of 24 hours. The calculated reticulocyte percentage, based on a standard of 4 to 6 vials of Lilly's liver extract No. 343 by mouth would have been 20.4 and 34.4 per cent in Patients 1 and 2, respectively, and this peak would have been reached on the 7th or 8th day of therapy. According to the reports of Sturgis, Isaacs and Rennie,² and those of Minot, Murphy and Stetson,³ this is a most satisfactory response. In Case 1 the expected response (20.4 per cent) was reached within 68 hours, and a maximum of 49.5 per cent in 108 hours. In Case 2 the expected response (34.4 per cent) was reached within 68 hours and a maximum of 52.8 per cent in 88 hours. The responses noted

are much more significant when one considers that only slightly more than 1 vial of Lilly's liver extract No. 343 was given, and this was made from 100 gm. of fresh liver, which amount has little or no therapeutic value when administered orally.

Two of the cases reported by Castle and Taylor with initial red blood cell counts of 980,000 and 1,490,000 per c.mm. had reticulocyte responses of 27.8 and 25.4 per cent, respectively. The calculated maximum reticulocyte responses were 34.6 and 22.3 per cent, respectively. In comparable cases of Sturgis and Riddle, 15 to 30 times the amounts which were given intravenously were necessary for oral administration to obtain equally good results. The importance of these responses has been judged according to the standards obtained from the work of Minot and his associates, who calculated their results from the data obtained in studying a group of cases with varying degrees of anemia. In comparison with these standards, the responses obtained in Patients 1 and 2 were more than satisfactory. However, if intravenous liver therapy is to be used, it seems highly probable that a new series of standards will have to be calculated.⁴

In addition to the magnitude and rate of change of the reticulocyte response, 4 hourly variations were also noted. On one occasion there was a 36 per cent difference in the reticulocyte count within a 24-hour period. This daily fluctuation was reported by Porter and Irving⁵ and Riddle and Sturgis.⁶ Apparently the variation is the result of some physiologic process which governs the metabolic activity of the bone marrow, but its significance may be questioned by a consideration of the factor of error in estimating the reticulocyte count. Inasmuch as the limit of error has not been determined, this factor remains an open question.

In Patient 1 there occurred an increase per c.mm. of 1,000,000 red blood cells in 10 days and 2,000,000 red blood cells in 15 days. In the same periods of time the hemoglobin percentage increased 24 per cent and 27 per cent above its original level. In Patient 2 there occurred an increase of 1,000,000 red blood cells within a 10-day period with a hemoglobin increase of 28 per cent (Tables 1 and 2). Similar data were also obtained in the case reports of Riddle and Sturgis and Porter and Irving.

A mild leukocytosis was observed in both cases at infrequent intervals during treatment. The temporary increase in the white blood cell count was reported by Riddle and Sturgis and was considered by them as a bone marrow stimulation phenomenon. Inasmuch as neither patient had any concomitant signs or symptoms of infection, the stimulation of the bone marrow undoubtedly accounts for the transient increase of the white blood cell count. Careful study of serial blood films showed a temporary increase in the peripheral circulation of all the elements of the marrow. The platelets were markedly increased in number with the presence of

TABLE 1.—SUMMARY OF BLOOD FINDINGS—PATIENT 1.

Date.	Red blood cell count.	White blood cell count.	Hemoglobin, per cent.	Reticulo-cyte count.	Hours of treatment.
May 25	1.57	5800	41	2.7	-24
26	1.43	2650	45	2.0	
26 2 P.M.	1.59	2900	47	4.4	2
8 P.M.	1.40	1650	47	3.0	8
27 Midnight	3.2	12
4 A.M.	3.8	16
8 A.M.	1.40	7600	41	3.7	20
NOON	3.4	24
4 P.M.	4.7	28
8 P.M.	1.54	4300	39	5.0	32
28 Midnight	6.4	36
4 A.M.	3.7	40
8 A.M.	1.66	7400	51	6.7	44
NOON	11.8	48
4 P.M.	16.8	52
8 P.M.	1.79	6300	44	13.2	56
29 Midnight	16.7	60
4 A.M.	18.8	64
8 A.M.	1.93	8000	45	21.7	68
NOON	21.1	72
4 P.M.	25.8	76
8 P.M.	2.00	6450	51	28.2	80
30 Midnight	27.5	84
4 A.M.	38.9	88
8 A.M.	1.88	6300	48	38.0	92
NOON	42.6	96
4 P.M.	45.0	100
8 P.M.	1.87	4300	51	46.3	104
31 Midnight	49.5	108
4 A.M.	38.0	112
8 A.M.	1.96	8600	47	38.2	116
NOON	42.0	120
4 P.M.	25.5	124
8 P.M.	2.17	6400	51	31.4	128
June 1 Midnight	25.8	132
4 A.M.	26.4	136
8 A.M.	2.26	7650	49	35.3	140
NOON	27.4	144
4 P.M.	31.8	148
8 P.M.	2.87	4550	53	24.3	152
2 Midnight	20.0	156
4 A.M.	13.5	160
8 A.M.	2.90	7900	53	21.3	164
NOON	14.7	168
4 P.M.	172
8 P.M.	2.12	3450	53	12.5	176
June 3 Midnight	16.3	180
4 A.M.	9.6	184
8 A.M.	2.23	5850	57	16.9	188
NOON	12.3	192
4 P.M.	13.9	196
8 P.M.	2.13	4050	60	14.1	200
4 Midnight	11.7	204
4 A.M.	12.8	208
8 A.M.	2.61	8800	58	14.3	212
NOON	11.8	216
4 P.M.	16.5	220
8 P.M.	2.60	3300	65	12.6	224
5 Midnight	10.9	228
4 A.M.	11.3	232
8 A.M.	2.77	9.6	236
NOON	14.3	240
4 P.M.	9.9	244
6 8 A.M.	2.68	9950	61	13.0	260
7 8 A.M.	2.91	6000	66	7.8	284
8 8 A.M.	3.73	10,000	69	3.9	308

TABLE 2.—SUMMARY OF BLOOD FINDINGS—PATIENT 2.

Date.	Red blood cell count.	White blood cell count.	Hemo-globin, per cent.	Reticulo-cyte count.	Hours of treatment.
June 1	0.98	3,600	15	3.7	-24
2 3 P.M.	1.11	4,900	22	4.2	
4 P.M.	1.08	2,050	22	5.5	
8 P.M.	0.86	1,250	21	5.2	4
3 Midnight	5.1	8
4 A.M.	4.4	12
8 A.M.	0.94	5,100	20	6.7	16
NOON	4.4	20
4 P.M.	3.7	24
8 P.M.	0.75	3,950	19	7.2	28
4 Midnight	7.3	32
4 A.M.	9.5	36
8 A.M.	1.03	5,400	25	12.9	40
NOON	9.4	44
4 P.M.	0.76	7,800	21	9.0	48
8 P.M.	1.11	8,600	26	17.0	52
5 Midnight	12.7	56
4 A.M.	29.4	60
8 A.M.	1.16	13,500	28	31.0	64
NOON	32.7	68
4 P.M.	48.9	72
8 P.M.	1.02	6,000	27	..	76
6 Midnight	47.0	80
4 A.M.	39.4+	84
8 A.M.	1.23	6,100	29	52.9	88
NOON	49.5	92
4 P.M.	44.9+	96
8 P.M.	1.23	2,950	31	..	100
7 Midnight	29.4+	104
4 A.M.	49.0	108
8 A.M.	1.25	4,300	32	49.7	112
NOON	43.6	116
4 P.M.	120
8 P.M.	1.30	3,450	32	45.1+	124
8 Midnight	51.3	128
4 A.M.	46.9	132
8 A.M.	1.64	4,550	34	33.6	136
NOON	36.4	140
4 P.M.	41.5	144
8 P.M.	1.48	3,650	35	50.3+	148
9 Midnight	48.5	152
4 A.M.	43.3	156
8 A.M.	1.56	6,800	38	22.1	160
NOON	164
4 P.M.	39.1	168
8 P.M.	1.78	5,950	38	..	172
10 Midnight	176
4 A.M.	3	38.8	180
8 A.M.	1.99	10,700	42	29.3	184
NOON	35.0	188
4 P.M.	36.3	192
8 P.M.	1.43	6,550	43	21.1	196
11 Midnight	22.4	200
4 A.M.	13.6	204
8 A.M.	1.84	8,400	45	17.0	208
NOON	19.4	212
4 P.M.	9.6	216
8 P.M.	1.40	6,400	43	14.5	220
12 Midnight	15.0	224
4 A.M.	16.1	228
8 A.M.	1.89	8,050	45	11.6	232
NOON	15.5	236
4 P.M.	16.3	240
8 P.M.	1.73	5,800	44	14.6	244
13 Midnight	12.3	248
4 A.M.	9.3	252
8 A.M.	1.67	9,900	44	14.5	256
NOON	13.9	260
4 P.M.	9.2	264
8 P.M.	2.08	7,200	43	16.6	268
14 Midnight	12.6	272
4 A.M.	8.0	276
8 A.M.	2.22	7,200	49	7.8	280
NOON	12.0	284
4 P.M.	288
8 P.M.	1.92	5,950	47	..	292
15 Midnight	12.2	296
4 A.M.	6.0	300
8 A.M.	2.16	14,700	45	5.9	304
NOON	5.6	308
4 P.M.	7.0	312
8 P.M.	316

many giant forms; there was a "shift to the left" in the myeloid series with all types of cells being present in an increased amount; the red cells showed all forms of immaturity from blast cells through the various stages to mature cells. This crisis may be due to a clearing of the liver and spleen, which resume their fetal hemopoietic function during the relapse in severe cases of pernicious anemia, as well as to stimulation of the bone marrow.

Clinical Effects. The clinical effects noted in both patients were striking in their similarity. They may be classified into two groups: (a) The immediate effects as a result of the injection; (b) changes noted with clinical improvement following adequate therapy. The picture during and immediately following the injection is characteristic of a systemic reaction to histamin or cholin. The patients described a sensation of warmth over the entire body, especially the face. Accompanying this was a choking sensation, a feeling of air hunger or a sense of marked pressure over the chest. There was a throbbing sensation in the head, the face became flushed and large beads of perspiration were observed over the forehead and about the mouth. These symptoms were transient, apparently could be somewhat influenced by the rate of injection and disappeared entirely with cessation of the injection.

Within a period of 45 to 60 minutes, the patients were suddenly seized with a severe chill. The rigor lasted for 90 minutes in Patient 1 and 30 minutes in Patient 2, and slowly abated. The temperature gradually mounted to 104° F. in Patient 1 and 102° F. in Patient 2. Accompanying the chill, Patient 1 had a severe vomiting spell, became cyanotic and complained bitterly of numbness of his fingers and hands. Within 24 hours all these symptoms had disappeared.

From this period on the clinical improvement compared more than favorably with those patients who received small daily doses of liver extract orally. The usual increase of appetite, strength and sense of wellbeing, as well as the decrease of pallor and icterus, took place much more rapidly with the intravenous therapy. With the oral administration of liver extract, the clinical improvement is usually seen in 72 to 96 hours. The 2 patients who received the extract intravenously showed evidence of clinical improvement within 48 hours.

Perhaps the most striking effect with the above intravenous preparations is the immediate lowering of the blood pressure, a phenomenon pointed out by Cohn, Minot and their associates, and Castle and Taylor. In Patient 1, 1 cc. of 1 to 1000 solution of adrenalin was given hypodermically 10 minutes before the intravenous therapy in order to counteract this depressor substance. Apparently it had no effect, the blood pressure falling from 155 to 90 systolic and from 85 to 50 diastolic, within 3 hours. The diastolic pressure returned to normal in 3 hours, whereas the systolic pressure re-

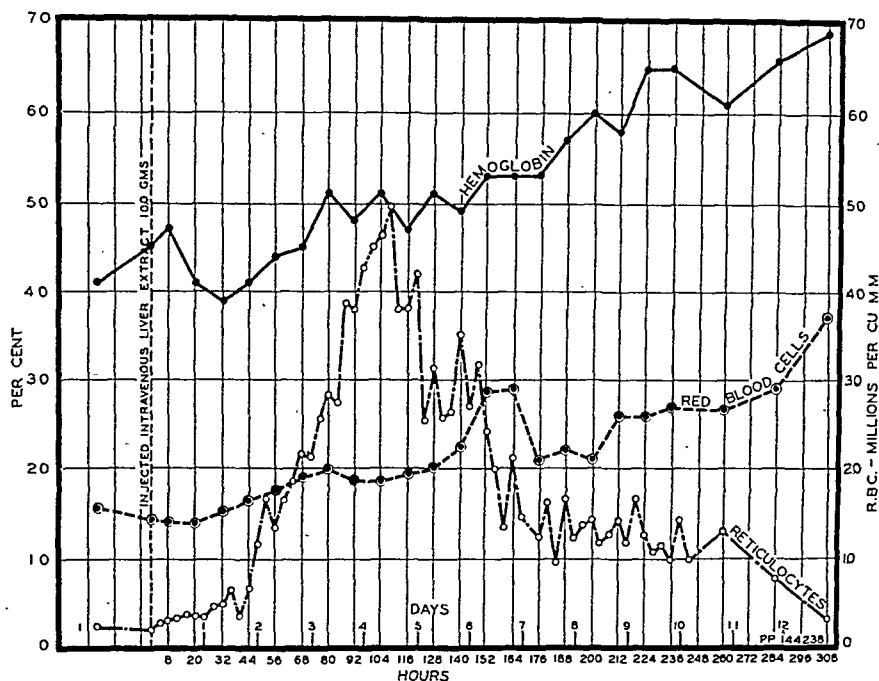


CHART I.—Response to single injection of liver extract intravenously (unrefined).

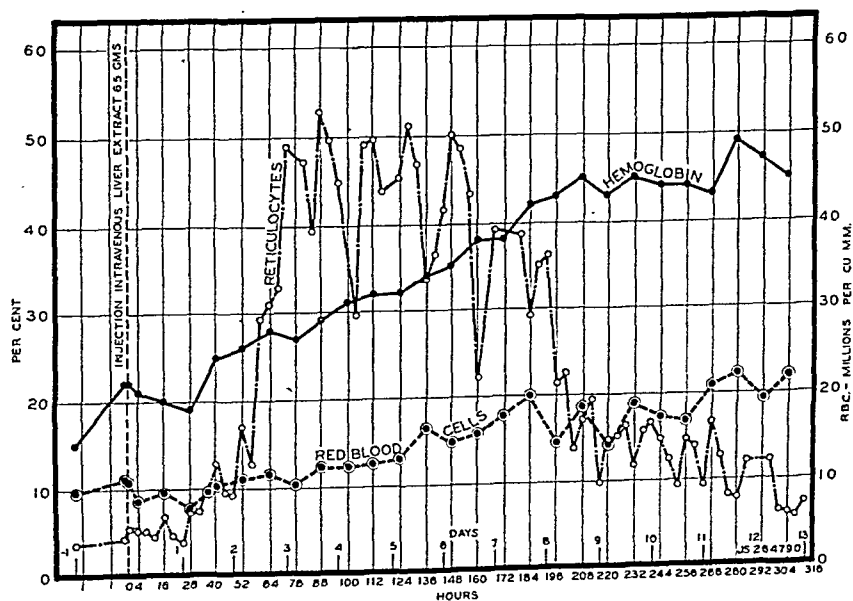


CHART II.—Response to single injection of liver extract intravenously (unrefined).

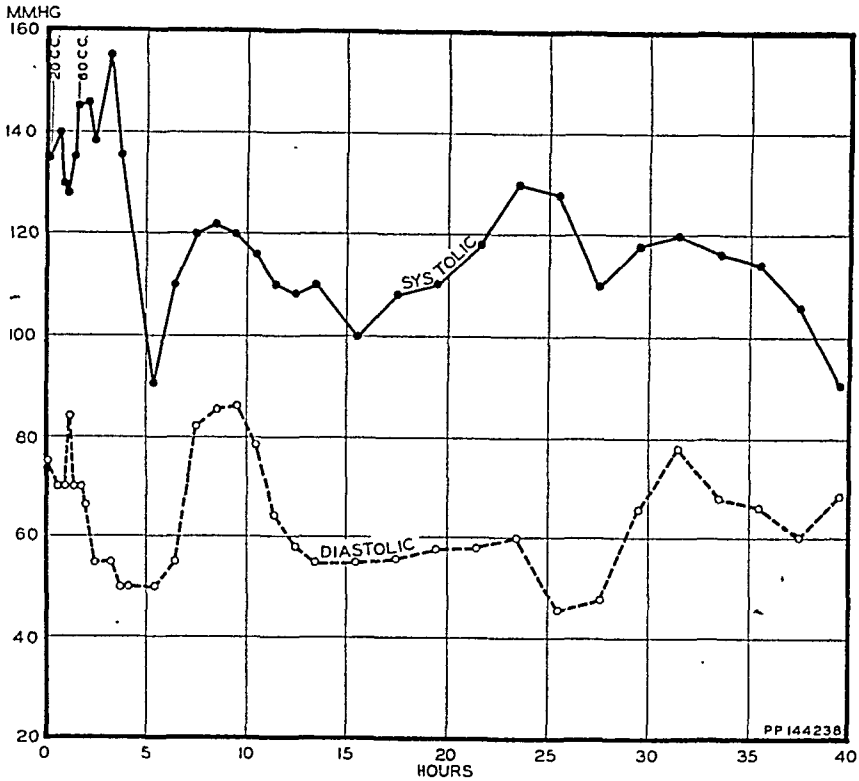


CHART III.—Blood pressure following intravenous injection of liver extract (unrefined).

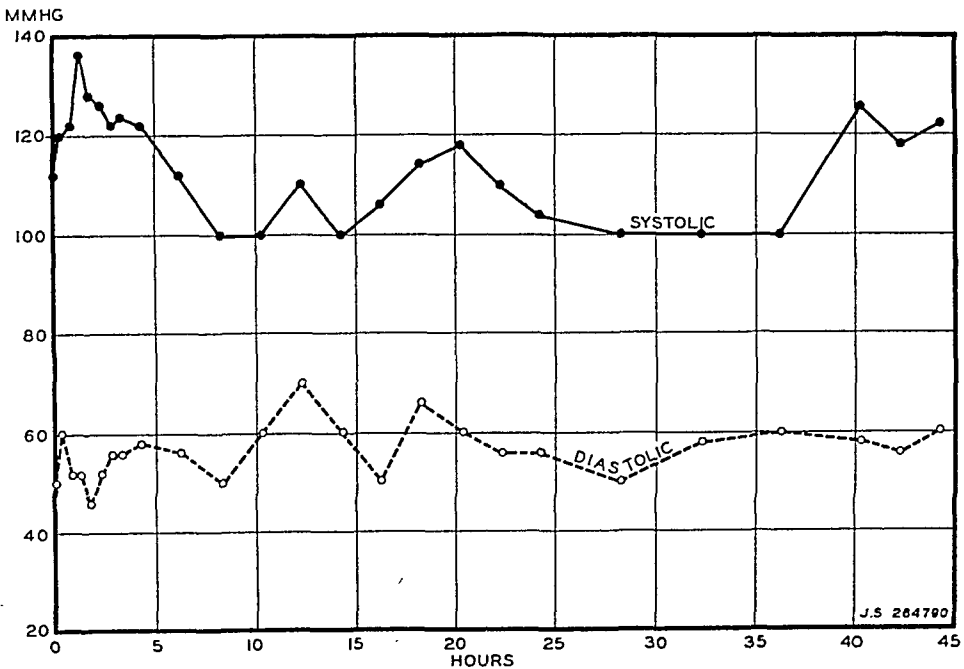


CHART IV.—Blood pressure following intravenous injection of liver extract (unrefined).

mained at a lower level for 2 days. In Patient 2 the systolic pressure was reduced from 120 to 100 in 8 hours and the diastolic pressure from 60 to 46 in 2 hours. The systolic pressure remained lowered for 2 days and the diastolic pressure returned to its original level in 8 hours. The prolongation of the hypotensive effect is in contrast to the observations of Castle and Taylor, who reported a return of the blood pressure to its original level within 1 to 2 minutes after the termination of the injection. The course of the blood pressure of Patients 1 and 2 are shown in Charts III and IV. Although the blood pressure is lower during sleep,⁷ there is little question that the initial drop was due to the injection of the unrefined liver extract.

Discussion. The use of liver extract intravenously as an effective therapeutic measure in the treatment of pernicious anemia brings up many new and interesting problems. Intravenous therapy causes a more rapid response with a much smaller dosage, and the response obtained, if measured in terms of reticulocyte percentage, is much more effective than any form of liver treatment by mouth. If we accept the theory that pernicious anemia is a deficiency disease and that the substance lacking is present in both liver and ventriculin, or is generated by the latter, it may be possible to explain the mechanism by which the various substances act in the effective treatment of this malady, and their speed of action.

Food entering the gastro-intestinal tract is broken down into its various components, one of which is the unknown antianemic substance. This product or its precursors is probably formed in the stomach, since its presence there has been proven. From here it is transported to the bone marrow for utilization in the manufacture of red blood cells. The excess is probably stored in the liver⁸ in much the same manner as glycogen. Such a hypothesis is much more plausible than the assumption that the unknown substance is made in the liver and then transmitted to the stomach for secretion or further distribution. It is just one step more to the conclusion that intravenous liver preparations contain the active principle, which is supplied to the body through the blood, in a free and concentrated form. If this same liver is given by mouth, greater quantities would be necessary as much of the antianemic substance would probably be lost in the digestive process. When liver extract is given intravenously it is given in a form which is ready to be used immediately by the bone marrow, hence the early response.

Up to the present time it has been impossible to make an effective intravenous preparation from ventriculin. From the results obtained it is believed that the active principle, although generated in the stomach, does not exist in a free state in the dried stomach tissue as in the liver, but rather is bound up in some form which, when freed from protein, loses its potency or is present in the form of a precursor.⁹

The marked difference between the effect of a small amount of liver extract intravenously and the same amount by mouth probably lies in the rate of absorption. The liver extract when given orally is either absorbed with difficulty, partially destroyed, or the activity is delayed until the concentration in the tissues reaches a certain optimum. This accounts for the extremely rapid increase in red blood cells and hemoglobin with intravenous therapy, which is not seen with oral administration.

It would appear that intravenous liver therapy would be the most economical form of treatment in pernicious anemia. In the beginning it was hoped that intravenous therapy might be a suitable substitute for transfusion in an emergency. The one objection to this unrefined liver extract is the severe body reaction. It is unjustifiable to increase a patient's discomfort and to aggravate his already poor condition. If the reaction were slight or entirely eliminated by using a purified preparation, it could be used as a satisfactory therapeutic measure. More recently a refined liver extract has been prepared at the Simpson Memorial Institute which has a high degree of potency and does not produce untoward effects. The results following the use of this preparation will be reported in a later article.

Conclusions. 1. Two cases of pernicious anemia treated with liver extract intravenously are reported, in which a maximum reticulocyte response was produced in a shorter time than orally with a dosage which would have been wholly inadequate if taken by mouth.

2. The reticulocyte response began within 24 hours following liver extract therapy; the maximum was reached in 88 and 108 hours (Patients 1 and 2). The return to the pre-treatment level occurred in 264 hours (11 days).

3. The red blood cell count in Patient 1 increased 1,000,000 cells in 10 days, with a corresponding increase of 24 per cent hemoglobin. In the second patient there was also an increase of 1,000,000 cells in 10 days, with a hemoglobin increase of 28 per cent.

4. Lilly's Liver Extract (0.1 gm. per kg. body weight), when given intravenously, produces an effect lasting at least 2 weeks.

5. The liver extract used in these experiments is not suitable for clinical use because of the reactions.

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A CLINICAL METHOD OF MEASURING RED CELL DIAMETERS BY DIFFRACTION.*

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HURST's¹ statement that "the most characteristic features of the blood in Addison's anemia are the anisocytosis and the increase in the average size of the red cells," has been substantiated by many workers using various methods of mensuration. Naturally there is some disagreement among the proponents of the several methods, particularly as to the necessity of measuring cells in plasma^{2,3} or in a dried smear,⁴ but from a purely practical viewpoint, a simple, rapid method of sufficient accuracy for clinical purposes is a desideratum.

The direct^{5,6} method, using an ocular micrometer, gives the extremes and the mean from which a curve may be constructed.⁷ However, it has disadvantages, not the least of which is that it is too tedious and time consuming for routine clinical use.

Another method is the measurement of photographically enlarged cells, which gives the same information as that obtained by the direct method. While somewhat less tedious it requires accurate magnification and good photography, and is also too time consuming for clinical use. The same objections apply to various modifications, such as projection on to a ruled screen, or use of the Euscope.⁸

The third method makes use of the hematocrit to obtain the total volume of cells in a given amount of blood, and dividing this volume by the number of cells per cubic millimeter will give the average cell volume. There are several modifications of this method,^{9,10} but all require time for careful and repeated counts, and accurate observations of total volume, and even then there is the possibility of cumulative errors.

The fourth method uses the phenomenon of diffraction, first applied by Young (1773-1829) for the measuring of wool fibers. However, to Pijper^{11,12,13} belongs the credit for the first practical application of this method to obtain red cell diameters. The principle consists in passing a beam of parallel rays of white light through a thin blood smear, and as the rays strike the periphery of each cell they are bent in toward the cell and also split into the component colors, so as to form concentric rings of the primary colors of the spectrum, ranging from violet in the center to red of the outermost circle in each series. These rings are repeated in sequence in the second series and so on.

The angle formed by the diffraction of the light rays is dependent

* Publication approved by the Surgeon-General, U. S. A.

upon the wave length of the color chosen, so that the size of the spectrum formed is in definite relation to the size of the cells and the distance of the screen upon which the spectrum is caught. Since the rays are bent inward, the size of the spectrum is in inverse proportion to the size of the cells.

Without going into details, the system of Pijper requires a suitable series of lenses to produce parallel(?) rays of light, an evenly made smear of cells, a collecting lens and finally a screen. The diameter of the ring of the color chosen is then measured and the calculation made from the following formula: $D = \frac{L \sqrt{F^2 + R^2}}{R}$ where D = diameter of the cells, L = wave length of the color used, F = the focal distance of the lens, and R = the radius of the spectrum.

Objections may be raised concerning the measurement of diameters, the effect of drying,¹⁴ and so on, nevertheless granting all these objections, the fact remains that there is a decided difference between the spectrum produced by large, and that produced by small cells, a fact which may be verified by control measurements with the ocular micrometer, or other methods.

The use of Pijper's application is simple and inexpensive, but requires suitable space and a dark room. Moreover, the measurement of the circles with dividers is subject to error because the dividing line between colors is not clean cut. The writer knows of two ingenious modifications of Pijper's method, one by Emmons¹⁵ and one by Eve,¹⁶ the latter being in use in this laboratory.

The instrument about to be described is still another modification of the same principle for which only simplicity is claimed. There are no batteries, parallelizing lenses nor lamps costly or difficult to obtain.

This instrument occupies the upper end of the tube of a monocular microscope, the ocular having been removed. One objective is removed, as is the condenser and in place of the latter a light is inserted. On each side of the stage of the instrument is a millimeter scale with vernier, registering the position of a sliding shutter controlled by a thumbscrew (Fig. 1).

A properly made smear is placed, smear side down, on the stage and viewed through the pinhole ocular and the shutters set as nearly as possible at the extreme periphery of the red circle of the first series. The readings on each side are added, the result being the diameter of the spectrum. A table gives the corresponding approximate average cell diameter in microns; the whole procedure requiring about 30 seconds. This instrument has been used on hundreds of slides and has proved to be rapid, easy to use and practically foolproof. A smear of each case showing erythropenia is first observed with this instrument, and if the spectrum is smaller than normal, other methods are used to confirm the findings. If the

spectrum is smaller than normal it is advisable to examine the smear with the high dry to rule out rouleaux formation, for the cells must be evenly distributed on one plane. If too close together, superimposed or widely separated the result will not be satisfactory. A properly made smear produces a spectrum which at its center shows a small bright area of light occupying the position of violet, then a surrounding zone of pale yellow merging into yellow, orange and red, then the second series beginning with blue (Fig. 2).

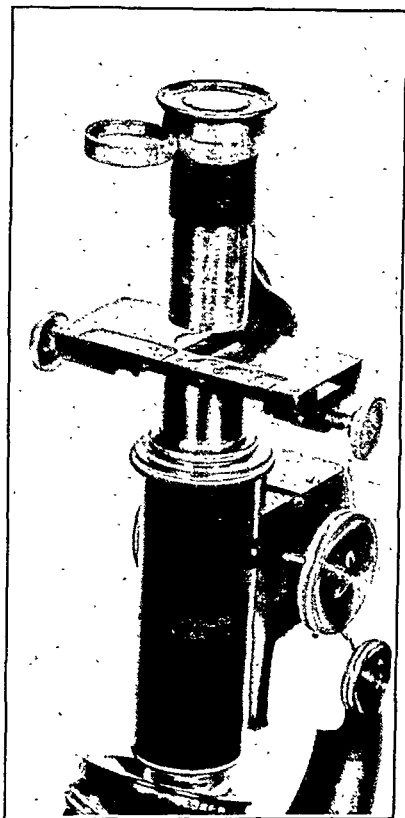


FIG. 1.—Showing mounting of instrument; the shutters, and thumbscrews which control them, and the vernier scales.

If a marked poikilocytosis is present, then even in a properly made smear the spectrum will appear diffuse and without the clean cut colors of the normal spectrum, due to the unequal and distorted diffraction, nevertheless the spectrum may often be measured with a satisfactory degree of accuracy (Fig. 3).

While textbooks of physics have been freely consulted and the opinions of physicists obtained, the writer is particularly indebted to Mr. Harry G. Ott for his interest and assistance in solving the

physics and mathematics involved. The conclusions reached are as follows: In this instrument the light from a pinhole at a standard distance falls on the smear. This light is, in a sense, bent by diffraction around each of the corpuscles of the smear, at a definite angle

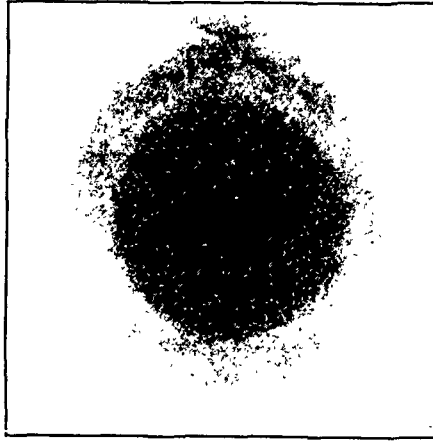


FIG. 2.—Halo of normal cells.

for each wave length and corpuscle size. This bending changes the direction of some of the light, so that it will be sent through an observing pinhole above the smear. Each corpuscle of the aggregate contributes its own portion of light, all of these overlapping to form a nearly evenly illuminated halo. The size of the halo will be determined, at the smear, by the corpuscle farthest from the axis of the instrument that can send light through the observing

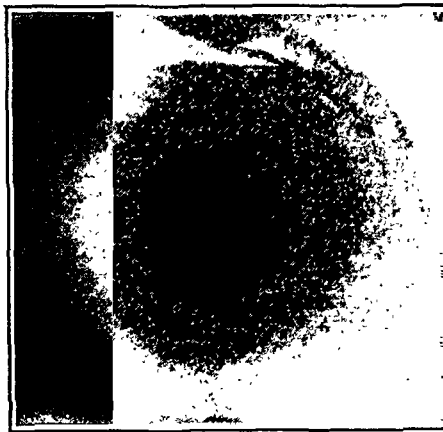


FIG. 3.—Halo of large cells, decidedly smaller and more diffuse, due to poikilocytosis.

pinhole. This is determined by the angle through which the light is bent by diffraction around the corpuscle. There is not an even distribution of light for all angles around the corpuscle. The intensity rises to maxima for certain angles, with minima of practically zero

intensity between. These minima serve to form a definite boundary to the halo formed by the maxima just preceding them. The first, and the brightest maximum formed by diffraction, lies at an angle between the two edges of the portion of the beam that is bounded by the corpuscle, and bent in such a direction as to pass through the observing pinhole. Let X = the pinhole source of

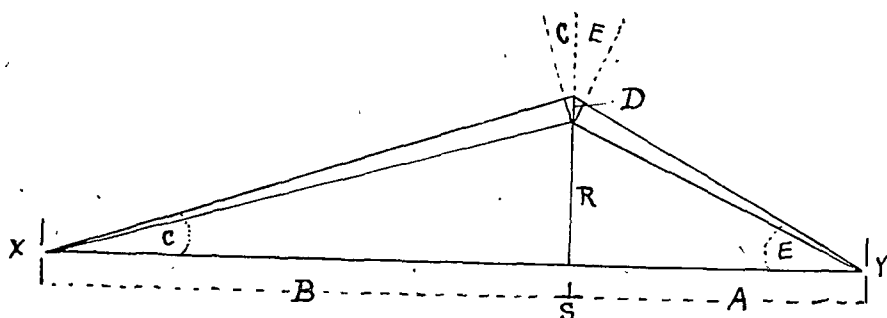


CHART I.

light, Y = the observing pinhole, D = diameter of corpuscle, R = radius of spectrum, L = wave length of light used, B = distance between illuminating pinhole and S , A = distance between observing pinhole and S , S = position of smear. The necessary difference in path of one wave length will be, $D \sin E + D \sin C = L$. But the angles are so small that the tangent and sine may be used interchangeably without significant error, hence the equation may be expressed:

$$D (\tan E + \tan C) = L$$

but

$$\tan E = \frac{R}{A} \text{ and } \tan C = \frac{R}{B}$$

so

$$DR \left[\frac{1}{A} + \frac{1}{B} \right] = L$$

or

$$D = \frac{L}{R} \frac{AB}{A+B}$$

It can be seen from the above equation that for a certain size of corpuscle, the size of the halo varies directly as the wave length.

TABLE 1.—DIAMETERS OBTAINED BY PHOTOGRAPHIC AND BY MICRODIFFRACTOMETER METHODS.

No.	Photographic.	Microdiffractor.	Difference.
1	6.6 μ	6.6 μ	0.0 μ
2	8.0 μ	7.5 μ	0.5 μ
3	8.1 μ	7.7 μ	0.4 μ
4	8.0 μ	8.0 μ	0.0 μ
5	9.3 μ	8.7 μ	0.6 μ
6	9.2 μ	9.0 μ	0.2 μ
7	9.3 μ	9.3 μ	0.0 μ
8	9.3 μ	9.3 μ	0.0 μ
9	9.9 μ	9.8 μ	0.1 μ
10	10.4 μ	10.1 μ	0.3 μ

Acknowledgement is made of the coöperation of the Spencer Lens Company in meeting the mechanical difficulties.

Summary. A brief survey of various methods of red cell measurement is given.

A description and use of a simple micro-diffractometer using the phenomenon of diffraction for the measurement of erythrocyte diameters.

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THE EFFECT OF SPINAL DEFORMITIES ON THE HEART.

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CARDIAC signs and symptoms resulting from deformities of the spine have been emphasized by Continental writers. However, the English and the American literature upon this subject is meager. Finley¹ has recently reported 4 cases of severe kyphoscoliosis, resulting in hypertrophy and dilatation of the heart with cardiac insufficiency and death. Reid² also reported a case of scoliosis causing cardiac hypertrophy and dilatation.

The material on which this study is based consists of 26 cases of spinal deformities, mostly of severe grade, involving the cervical or dorsal regions.* They were divided as follows: kyphoscoliosis, 15 (left, 1; right, 14); scoliosis, 5 (left, 2; right, 3); kyphosis, 4; lordosis, 2.

A history was taken and physical examination performed on all patients. The age, sex, spinal deformity and etiology are listed in

* Some of these patients were observed through the courtesy of Dr. A. M. Rechtman.

Table 1. One patient died of uremia; the remainder are alive, although some are incapacitated. The heart was studied fluoroscopically and orthodiagrams drawn in all but 3 cases; in the latter, 6-foot films were taken. Electrocardiograms were taken in 24 cases.

Scoliosis and Kyphoscoliosis. According to Vaquez,³ Delpech, in 1848, was the first to record the association of spinal deformities with cardiac symptoms. However, Hippocrates,⁸ in discussing gibbositities in his chapter on articulation, speaks of dyspnea as a common symptom "in those cases where the gibbosity is above the diaphragm." De Sauvages, Cullen and Bouvier, according to Boas,⁴ have noted cardiac and respiratory disturbances in kyphoscoliosis, and in 1865 Sottas published a thesis on the effect of deviations of the vertebræ on the functions of respiration and circulation. Since that time the French and Germans have contributed many articles on the cardiac pathology and symptomatology of scoliosis and kyphoscoliosis, but the monograph of Bachmann⁵ is the outstanding work on this subject.

TABLE 1.—CLASSIFICATION OF 26 CASES OF SPINAL DEFORMITIES.

	Age.						Sex.		Etiology.						
	1 to 9.	10 to 19.	20 to 29.	30 to 39.	40 to 49.	50.	Male.	Female.	Rickets.	Tuberculosis.	Poliomyelitis.	Muscular atrophy.	Empyema.	Dislocation of hip.	Unknown.
Kyphosis	..	1	2	1	0	4	..	4					
Scoliosis	1	1	2	1	1	4	1	1	..	3
Kyphoscoliosis	3	5	2	2	2	1	9	6	6	1	2	1	5
Lordosis	..	1	1	1	1	1	1
Total	4	8	5	3	4	2	11	15	7	5	2	1	1	1	9

Bachmann studied autopsy findings in 197 cases of his own and 79 cases collected from the literature. Cardiac abnormalities were found in 154 of 197 cases and, of these, 87 (56 per cent) had hypertrophy or dilatation of the right heart; in 27 (17.5 per cent) the left side was affected; in 40 (25.9 per cent) both sides. Displacement of the heart and kinking of the great vessels were noted in some cases. Similar findings have been reported by Romberg,⁶ Rieder⁷ and others. Death was due to heart failure in 116 (59.4 per cent) of 195 cases, but in 72 of these it was secondary to a pulmonary disorder.

Pathologic Physiology. Changes in the size and shape of the thorax and the consequent effect upon the lungs are doubtless the most important causes of the hypertrophy and dilatation of the right side of the heart noted in many of these cases. The lung on the side of the deformity is usually compressed, and, while it is merely atelectatic in many cases, Bachmann described it as a "tongue of fibrous tissue" in some of the marked cases. A compensatory emphysema on the opposite side further embarrasses the right heart. Since this deformity often begins in early life and is complete before bodily growth, the thorax lags somewhat behind and, as a result, the lung volume is diminished. Hippocrates⁸ noted this and believed it the cause of dyspnea. According to Finley, the capacity of the lungs has been found to be reduced 20 to 60 per cent. Furthermore, the chest wall is limited in movement, and in many cases the diaphragm alone moves in respiration, and frequently this muscle is distorted. Thus the respiratory pumping effect is limited, or entirely lost in kyphoscoliosis. Rieder⁷ believed that a faulty gaseous interchange occurs because of the various changes in the lungs. These factors may be presumed to burden the right heart. Aortic anomalies, such as alterations in its courses, twisting or kinking may burden the left heart.

Clinical Aspect. Scoliosis and kyphoscoliosis affecting the cervical and thoracic vertebræ are the most serious of the spinal deformities from the cardiovascular point of view. Mild cases produce very little change with the thorax, but in moderate and severe cases the changes are more marked. Some are relatively free of symptoms, and even with a severe deformity (Fig. 1) they may go on for many years, although dyspnea on exertion may be present. Most of the patients, however, present symptoms such as dyspnea, cyanosis and edema of the legs. These symptoms tend to progress in severity and a clinical picture suggesting right-sided heart failure often appears.¹

Although bronchitis and pneumonia are frequent complications, there was evidence of tuberculosis of the lungs in only 1 of our 26 cases; another has had one tuberculous kidney removed and since then has developed tuberculosis in the remaining kidney. However, the distortion of the thorax is so great that examination of the lungs is exceedingly difficult and perhaps misleading; the possibility, therefore, exists that some of the other cases might have tuberculosis of the lungs. There is considerable difference of opinion with respect to the frequency of tuberculosis in association with these chest deformities.^{5,10,11,12}

Interpretation of the physical findings is difficult. Expansion of the thorax is poor; in many cases the thorax is fixed. The lung on the side of the convexity may be atelectatic, and on the opposite side emphysematous; frequently both appear to be present in the same lung. The apex beat is often displaced. Percussion of car-

diac outlines is shown by orthodiagraphy frequently to be unreliable in severe cases of kyphoscoliosis. Apical systolic murmurs

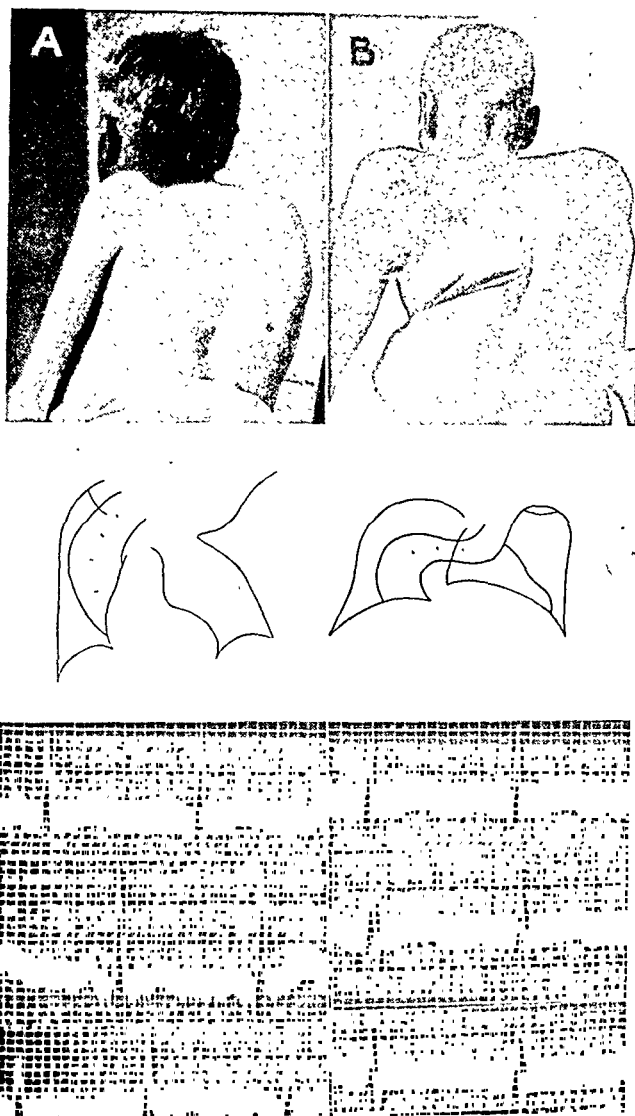


FIG. 1.—Two cases of severe right kyphoscoliosis in (A) a man, aged 35 years, and (B) a man, aged 61 years. Dyspnea on exertion was the outstanding symptom in both cases. Note the marked differences in shape and position of the heart. Orthodiagrams are anteroposterior views. The electrocardiograms show a normal electrical axis.

and accentuated pulmonic second sounds, especially in the severe cases, are common. Occasionally there is a rough systolic basal murmur, due possibly to a twist or kink of the aorta. Fig. 2 is

the orthodiagram of a case in which this possibility presented itself, for fluoroscopically the aorta seemed to make a sharp turn at the knob as it coursed downward and to the right to reach the spine. Substernal or precordial pain is an outstanding symptom in some cases.

Blood pressure variation between the two arms of more than 10 mm. of mercury occurred in 5 of the 15 cases of kyphoscoliosis. The greatest variation observed was 146 systolic and 86 diastolic in the right arm, and 104 systolic and 60 diastolic in the left. All cases, in which a difference of pressure was observed, had right kyphoscoliosis. In 3 cases the higher pressure was observed on the right side and in the other 3 cases on the left. Kinking or twisting of the aorta and its large branches may be concerned in this production of pressure differences, although they were absent in some of the severest cases.

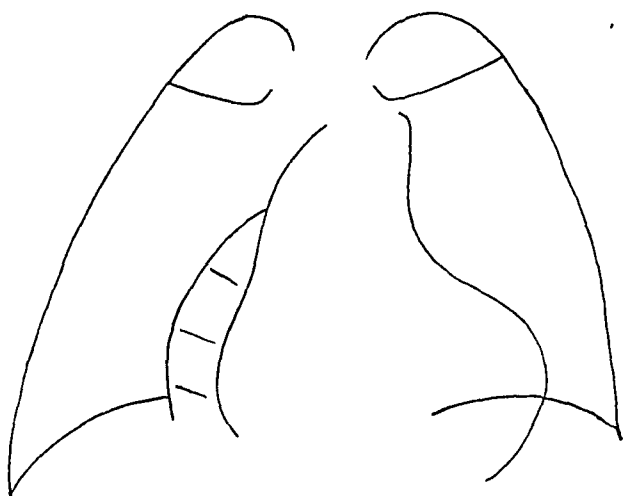


FIG. 2.—Orthodiagram of a woman, aged 38 years. Substernal pain was the chief complaint. Fluoroscopically the aorta appeared to make a sharp turn at the knob.

Cardiac rhythm was regular in all cases. Sottas reported cases of arrhythmia and Boas recently observed paroxysmal fibrillation in a young woman with scoliosis.

According to the literature, the vital capacity may be reduced as much as 65 per cent in severe cases, but in mild and moderate cases may be within normal limits. Flagstad and Kollman¹² found little reduction in cases involving the lower dorsal and lumbar regions.

Fluoroscopic Aspect. *Scoliosis.* The degree, level and direction of the curvature are important. High or middorsal scoliosis influences the heart more than lower dorsal deformity. Right scoliosis is by far the most common and is often complicated by some degree of kyphosis. The heart is displaced to the left; in some cases this is marked. In many cases of mild and moderate scoliosis the heart appears mitralized, the aortic knob small and, at times, the region

of the pulmonary artery prominent (Fig. 3, *A*). Brugsch¹³ noted this configuration in 80 per cent of his cases and believed it to be due to aplasia. Frequently, however, this configuration is not seen.

The "mitralization" appears to depend on two factors: (1) Enlargement of the right ventricle; (2) rotation of the heart as the result of the spinal deformity. Enlargement of the right ventricle occurs in the majority of cases and causes the heart to be rotated

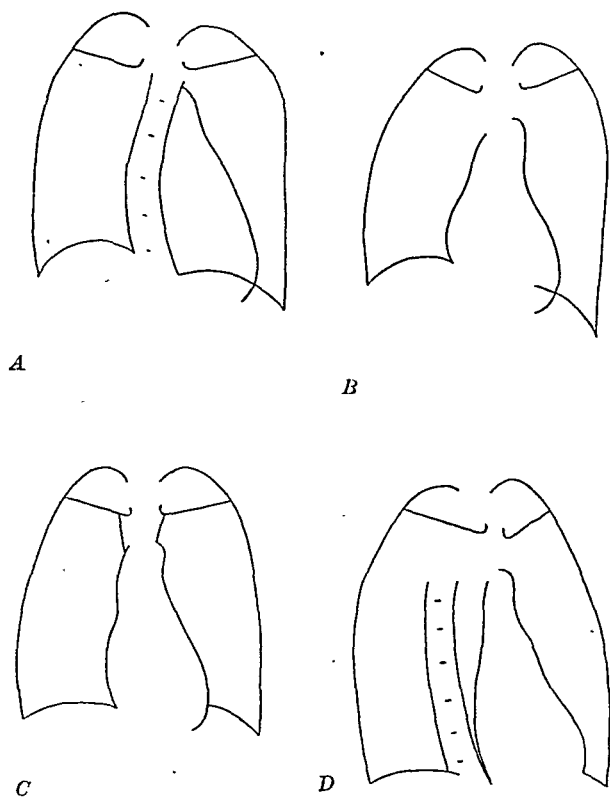


FIG. 3.—*A*, right scoliosis in a young man, aged 26 years; anteroposterior views; *B*, same patient in left anterior oblique 45 degrees; *C*, anteroposterior view of a normal young man, aged 26 years; *D*, after rotation to right anterior oblique 45 degrees. Note similarity of left borders in *A* and *D*.

upward, backward and to the left.¹⁴ This rotation is apparently partially responsible for the configuration of the left border both in mitral stenosis and scoliosis.

Direct rotation around the longitudinal axis may also be important, as is shown by rotating a patient with right scoliosis to the left until the spine appears straight. The heart shadow then resembles the normal anteroposterior shadow. Conversely, by rotating a normal person to the right until the spine appears curved,

the heart shadow frequently resembles that seen in the antero-posterior position in right scoliosis (Fig. 3, *A-D*).

Sometimes the aortic knob appears very sharp and prominent, probably due to the sharp bend taken by the aorta as it courses to the right to reach the spine, and to its better visualization since it is not obscured by the spine.¹⁷

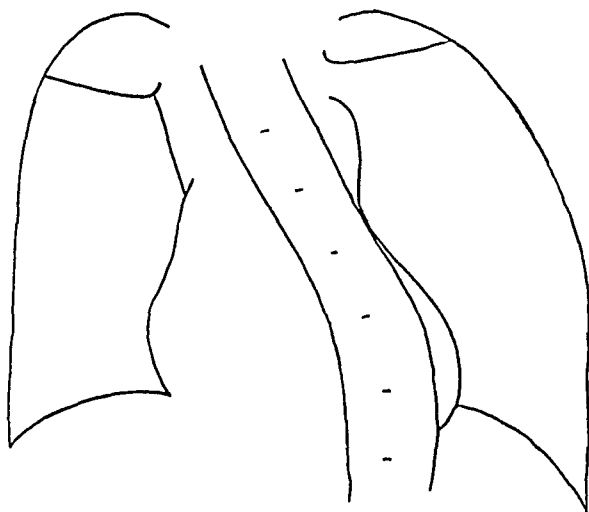


FIG. 4.—Left scoliosis in a boy, aged 7 years. Note the unusually wide aortic area and the central position of the heart. The shadow of the spine is within that of the heart.

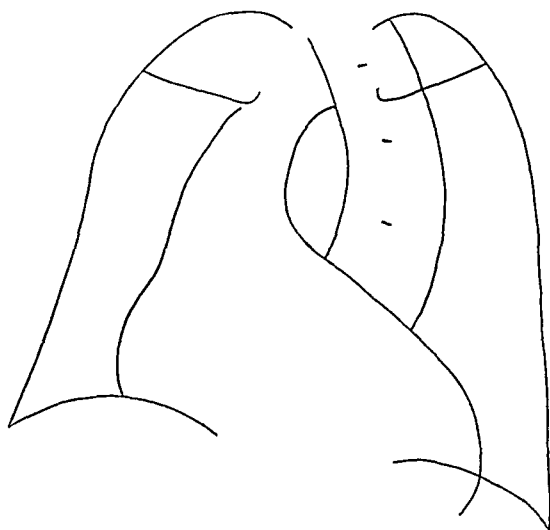


FIG. 5.—Left scoliosis, complicated by severe hypertension, in a man, aged 48 years. Note the "uncoiled" aorta and the clear space between the ascending aorta and spine. Descending aorta was not visualized.

In left scoliosis the heart assumes a more median position than normal and occasionally has the so-called aortic configuration. If the deformity is high, the aortic shadow appears considerably enlarged, for the aorta, in following the spine to the left, "uncoils"

itself (Figs. 4 and 5). Sometimes the descending aorta is seen projected alongside the ascending portion of the aorta. The aortic diameter, however, is not found widened. Low thoracic deformity will not cause a change in the aortic arch but the heart remains in the median position.

Kyphoscoliosis. Most cases of scoliosis are complicated by some degree of kyphosis. The configuration of the heart in these cases is usually not a combination of the effects seen in pure scoliosis and pure kyphosis, but is of a bizarre form and varies considerably from case to case (Fig. 1). Its form may be influenced by several factors, all of which are variable in their effect upon the heart. Among these are: (1) Spinal deformity and its consequent effect upon the bony thoracic cage; (2) hypertrophy and dilatation of the various chambers of the heart; (3) the height of the diaphragm; (4) coincident complications, such as hypertension and valvular disease.

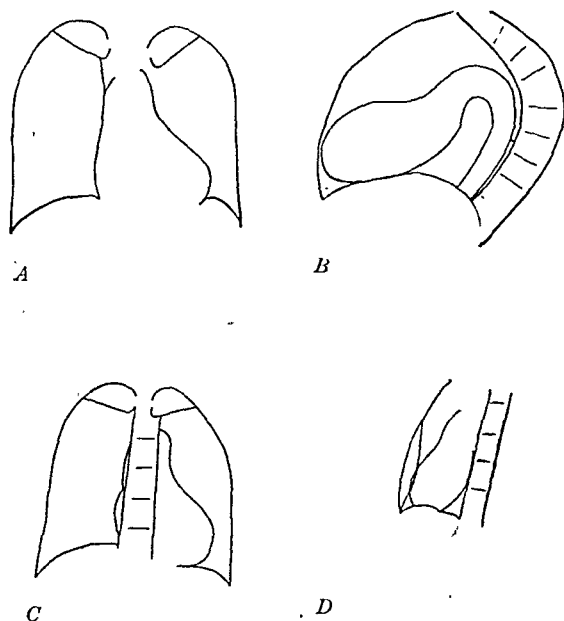


FIG. 6.—A, anteroposterior, and B, lateral views of a woman, aged 56 years, with kyphosis; C, anteroposterior, and D, lateral views of a boy, aged 9 years, with moderate funnel chest. All views have been reduced proportionately.

In severe cases the distortion of the thoracic cage is so great that the heart appears to assume a shape suitable to the space containing it, especially if the deformity occurs early in life when the organs have the greatest power of adaptability. This is exemplified by the contrast in shape of the heart in funnel chest and kyphosis; in the former the heart appears large but flat; in the latter, small

and long (Fig. 6, *A-D*). In kyphoscoliosis decrease of the anteroposterior diameter on one side and increase on the other side of the chest may be seen in the same patient, and its effect upon the heart will vary in different cases.

The deformity of the thorax also has a marked effect upon the diaphragm. In kyphoscoliosis the diaphragm is usually high and the effect further complicates the picture of a displaced and rotated heart of unusual shape.

Hypertrophy and dilatation of the various chambers of the heart will, of course, alter the cardiac silhouette. Factors concerned in the production of mitralization, such as right-sided enlargement and rotation, have been discussed above. Left-sided enlargement whether due to the deformity or to some coincident factor, such as hypertension, may also affect the cardiac silhouette (Fig. 5).

The position of the heart also varies from case to case. It is usually displaced to the left but in some cases it assumes a median position.

The transverse and descending aorta were visible in a few cases of right kyphoscoliosis. In each instance it crossed diagonally from its left position to reach the spine far to the right. In 2 cases observed postmortem, of which 1 is included in this series, the portion of the aorta which would normally be the descending aorta coursed directly to the right to reach the spine, and then closely followed its curve downward. Klawansky⁹ and Dwight¹⁸ have described cases in which a remarkable deformity of the aorta resulted from following a tortuous spine.

Electrocardiographic Aspect. Electrocardiograms were taken of 4 cases of scoliosis and 14 cases of kyphoscoliosis. Except for axis deviation the tracings were normal in 16 instances. The 2 abnormal electrocardiograms were from patients with kyphoscoliosis. In 1 the *Q-R-S* complex in Lead II was definitely split; in the other there was evidence of marked myocardial disease. The latter electrocardiogram, however, was from a patient with marked hypertension (190 systolic and 158 diastolic) and also a pituitary disorder. In no instance was there any disturbance in conduction, although Vaquez has noted defects in conduction in some of his cases.

Three cases of kyphoscoliosis and 2 of scoliosis showed a left axis deviation. One of the former, however, occurred in the case of hypertension mentioned above. One case of kyphoscoliosis showed a right axis deviation. The most marked cases, however (Fig. 1), showed a normal axis. Two possible explanations are offered for the infrequency of axis deviation, despite marked displacement of the heart.

1. In a small minority of cases the heart may be displaced as a whole without rotation on its anteroposterior or longitudinal axis.

2. Rotation of the heart around its longitudinal axis compensates for the rotation around the anteroposterior axis. According to

Meek and Wilson,¹⁵ displacement of the heart to the right or left usually causes a combined rotation on both axes and produces electrocardiographic changes which cannot be predicted, because of the opposing effects of simultaneous rotation around the anteroposterior and longitudinal axis.

Kyphosis. Pure kyphosis is relatively uncommon. According to the literature most of the patients do not present cardiac complaints. The increase in the anteroposterior diameter of the chest compensates for the decreased transverse and vertical diameters. The lung capacity is not reduced and there is little effect upon the circulatory system, although the shape and position of the heart and great vessels are considerably altered. Three of the 4 cases of kyphosis in this study presented cardiac symptoms, but in each case a complicating factor (hyperthyroidism in 2, arteriosclerosis and hypertension in 1) was probably responsible.

On fluoroscopic examination in the anteroposterior view, the heart appears small or normal in size, centrally placed and dense. In the lateral view it appears large. Thus its shape is altered, the anteroposterior diameter at times being greater than the transverse (Fig. 6, A-B). The arch of the aorta seems less rounded—in fact, almost flattened—as it extends posteriorly to follow the spine. The barium-filled esophagus which appears short in the anteroposterior view is seen to take a normal course.

Electrocardiograms were normal except for the fact that in 1 patient with hyperthyroidism auricular fibrillation was present.

Lordosis. Mild grades of lordosis are common, but have no effect upon the heart and are, therefore, not included in this study. Severe grades, affecting the thoracic spine, are uncommon unless complicated by some degree of scoliosis. According to Barie,¹⁶ many patients with lordosis do not present cardiovascular symptoms, although some complain of dyspnea on exertion. The 2 cases included in the present study had no cardiac symptoms. Both were, however, incapacitated from other causes.

According to Barie the heart is displaced to the left, but in our 2 cases no displacement was noted. The anteroposterior diameter of the heart in both cases was reduced, in 1 markedly (Fig. 7).

The electrocardiogram in 1 case (infectious arthritis) showed inverted *T* waves in Leads I and II. In the other, it was normal except for a left axis deviation.

Summary and Conclusions. 1. Spinal deformities, especially scoliosis, and kyphoscoliosis have a profound effect upon the lungs, and the effect upon the heart is probably secondary to the latter in most cases. Kinking or twisting of the great vessels as the result of displacement of the heart may be responsible for certain cardiac signs and symptoms.

2. Most patients with kyphoscoliosis and severe grades of scoliosis have signs of right-sided disturbance of cardiac function. How-

ever, they may live for years, many being restricted in activity because of dyspnea on exertion. Some are cyanotic and a few show edema of the legs. According to the literature most cases die of a pulmonary complication.

3. Kyphoscoliosis causes marked changes in the size, shape and position of the heart. The shape and position of the heart vary considerably from case to case.

4. The aorta tends to follow the spine in spite of the deformity. In 2 cases of right kyphoscoliosis observed postmortem the aorta coursed directly across the thorax to reach the spine.

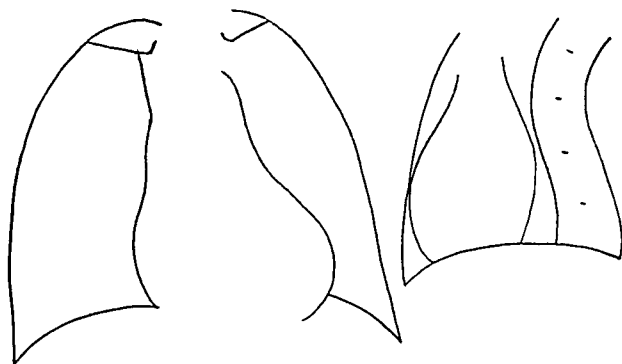


FIG. 7.—Anteroposterior and lateral views of a young boy, aged 10 years, with lordosis. Note the comparatively small anteroposterior diameter.

5. Pure scoliosis due to organic disease is relatively uncommon and is usually right-sided. In the latter the heart is displaced and often rotated to the left, causing it to appear “mitralized.” The aortic knob appears very sharp in some cases. Left scoliosis causes the heart to become centrally placed and the aortic area to appear widened. The aortic diameter, however, is not increased.

6. Three of the 4 cases of kyphosis included in this study presented cardiac complaints, but there were complicating factors in each case sufficient to account for the symptoms. In pure kyphosis the anteroposterior transverse diameter ratio tends to be greater than normal.

7. Two cases of lordosis presented no cardiac symptoms. The anteroposterior-transverse diameter ratio was smaller than normal in both.

8. Except for axis deviation in six instances, the electrocardiogram was normal in 20 of 24 cases of spinal deformity. Two of the 4 abnormal electrocardiograms were in patients with hyperthyroidism and hypertension. The infrequency of axis deviation despite displacement and rotation of the heart is probably due to the opposing effects of rotation around longitudinal and anteroposterior axes.

NOTE.—This study was undertaken at the suggestion of Dr. Stengel. Dr. Wolferth has made many valuable suggestions.

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CLINICAL OBSERVATIONS ON THE CAROTID SINUS REFLEX.

I. THE FREQUENCY AND THE DEGREE OF RESPONSE TO CAROTID SINUS PRESSURE UNDER VARIOUS DISEASED STATES.

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It has been known for many years that pressure on the carotid artery at the level of the cricoid cartilage would produce slowing of the heart. Perry¹ observed this phenomenon as long ago as 1779 in a case of hemiplegia. In 1868 Czermak² called attention to this reaction and quoted Pflüger, who first obtained this effect on vagal stimulation in animals. In the same year Sustschinsky³ showed that this vagal response in animals could be obtained in one of three ways: (1) by removal of the accelerator nerves; (2) by lessening the coronary blood supply to the heart; (3) by decreasing the ventilation of the blood.

Until recent years, the mechanism of the production of this reaction was considered to be a direct mechanical stimulation of the vagus nerve running in the carotid sheath. It was found, however, that in certain individuals, a minimum amount of pressure, insufficient to affect the vagus, produced results. Besides, Scherf⁴ suc-

ceeded in producing slowing of the heart by stimulation of the central end of the cut vagus in an individual who underwent a vagotomy operation for therapeutic purposes. It was, therefore, evident that it was a reflex rather than a direct vagal reaction which was responsible for the phenomenon.

The mechanism of this reflex remained to be worked out by Hering⁵ in a series of animal experiments. He showed that this reflex originates in the wall of the sinus of the internal carotid artery near its junction with the external carotid. The afferent fibers run in the glossopharyngeal nerve where they enter by a branch, termed by him the "Sinus Nerve" which starts in the sinus wall. Mechanical irritation of the sinus wall, either external or internal, results in two independent reflexes—one producing slowing of the heart and another a fall in blood pressure. The efferent impulse which slows the heart is carried by the vagus. Hering further showed that the sinus nerve has constant tonicity, for its severance results in a slight, permanent rise in blood pressure and pulse rate.

Although reflex slowing of the heart occurs in all experimental animals as well as in man by clamping the carotid sinus, ordinary mechanical stimulation caused by pressure upon the sinus area from without produces slowing only in a limited number of cases. It has been found to accompany various diseased states. Perry,¹ as said before, observed it in a case of hemiplegia. Czermak,² Quincke⁶ and De la Harpe⁷ found it in connection with cerebral disease. Concoto⁸ observed it in a case of epilepsy and arteriosclerosis and in another case of cardiac hypertrophy and endocarditis. DeCrenville⁹ observed it mainly in cerebral disease, less constantly in general arteriosclerosis, occasionally in convalescence from acute disease, but almost never in health. Wenckebach¹⁰ found marked response to very slight pressure to occur in very badly diseased hearts. Hering⁵ obtained active response in localized sclerosis of the carotid artery, especially at the sinus of the internal carotid, and quoted Koch who found localized sclerosis of the carotid sinus in 4 autopsy cases who presented a marked reaction during life. Danielopolu and Missirlin¹¹ considered an exaggerated reaction to pressure a valuable diagnostic means in chronic myocardial disease existing in a latent form. Braun and Samet¹² presented a series of cases with coronary disease that showed marked response. They also produced coronary lesions in animals and found that such lesions increased vagal response. Their conclusions were that heightened response to vagal stimulation is indicative of coronary disease and is of grave prognostic significance. Most of their patients who showed an exaggerated response died in a few weeks or months. Sanders¹³ found some response in normal persons.

It would seem, then, that this reflex vagal response accompanies certain pathologic conditions and may even occur in apparently normal individuals. Its importance as a diagnostic means in cardiac

disease, stressed particularly by Concoto,⁸ Wenckebach,¹⁰ Danielopolu and Missirlin,¹¹ and Braun and Samet¹² makes it of special interest. The test is a simple one and, if it has any value in diagnosis, it certainly deserves careful consideration and more widespread use.

With a view of determining the frequency of occurrence of this reflex in various diseased states and in an attempt to ascertain its diagnostic significance, I performed the test on a series of 345 cases obtained from the cardiac clinic and the ward service of the Harbor Hospital, the cardiac clinic of the New York Post-Graduate Hospital, the general medical ward service of the Coney Island Hospital, and from private practice. The cases were divided into the following five groups according to the main diagnosis: *Group I*, coronary artery disease with definite myocardial damage; *Group II*, hypertension and hypertensive heart disease; *Group III*, rheumatic heart disease; *Group IV*, patients with abnormal signs or symptoms referable to the heart, but showing no definite evidence of heart disease; *Group V*, general constitutional disease (non-cardiac). This paper is a preliminary report, dealing with the male and female response to carotid sinus pressure in the various groups, and the degree of such response in each group.

Detailed Analysis of Cases. *GROUP I* (115 cases). The predominant diagnosis was coronary sclerosis with definite evidence of more or less myocardial disease. Most of these cases showed evidence of general arteriosclerosis; 41 presented the anginal syndrome; 16 had attacks of coronary occlusion; 28 had no angina, but presented other evidence of coronary disease. In addition to coronary changes, 7 cases had chronic bronchitis, 2 diabetes, 1 bronchial asthma, 2 obesity, 8 were in the period of menopause, and 5 showed evidence of congestive heart failure.

GROUP II (56 cases). The predominant diagnosis was hypertension. Four cases showed evidence of aortic sclerosis with dilatation; 7 had coronary occlusion; 5 were in the menopause; 24 had considerable cardiac enlargement; 1 had mitral stenosis, probably of rheumatic origin; 1 had chronic nephritis; 2 cerebral sclerosis; 6 diabetes; 1 a diffuse aneurysm of the aorta; 1 had congestive heart failure; 4 had no complications or associated disease.

GROUP III (50 cases). This group comprised a variety of chronic rheumatic cardiovalvular disease. Only 5 cases had acute rheumatic cardiac involvement. Of the chronic cases there were 21 with mitral insufficiency and stenosis, 1 with mitral stenosis and aortic insufficiency, 10 with mitral stenosis, 6 with mitral insufficiency, 2 with aortic insufficiency, 1 with double mitral and aortic insufficiency, 1 with aortic stenosis, 1 with double mitral and aortic stenosis, and 1 with mitral and aortic insufficiency. Three cases were fibrillating, 5 cases showed evidence of congestive failure, 1 case of mitral stenosis showed first degree heart block.

GROUP IV. Predominantly neurocirculatory asthenia (58 cases). They showed some symptoms or signs referable to cardiovascular disturbances but no definite evidence of anatomic cardiac pathology and no definite etiology pointing to heart diseases. Twenty patients complained of precordial pain; 15 complained of asthenia, occasional palpitation and some shortness of breath on exertion; 2 had angioneurotic edema; 12 showed simple tachycardia, marked nervous irritability and vasomotor disturbances; 2 cases presented moderate thyrotoxicosis; 3 were diabetics; 4 presented disturbances incident to the menopause.

GROUP V. No cardiovascular disturbances (66 patients). Sixteen patients suffered from various forms of neurasthenia; 4 had marked obesity; 5 had chronic pulmonary tuberculosis, 2 of whom showed evidence of activity; 1 had Addison's disease; 2 had mild thyrotoxicosis; 4 suffered from gastro-duodenal ulcers, 6 from chronic cholecystitis; 1 from sacro-iliac arthritis; 1 had a pituitary tumor; 3 had chronic appendicitis; 1 chronic nephritis; 1 gastric carcinoma; 1 pyelonephritis; 1 cerebrospinal lues; 2 chronic bronchitis and bronchiectasis; 1 osteoarthritis of the knee joints; 2 bronchial asthma, and 1 was in convalescence from lobar pneumonia; 5 had no definite disease but complained of chronic constipation. Two of these had evidence of chronic foci of infection in the tonsils and sinuses.

Individual Group Response to Carotid Pressure. Table 1 represents the responses of males and females in the various groups to carotid sinus pressure. In each group we have the number of males and females examined—the total number responding with the percentage response, the number responding to both-sided pressure, the number responding to left-sided pressure only, and the number responding only to right-sided pressure. In a separate column is the average for all groups showing the above responses. Fig. 1 is a graphic representation of the percentage response in the various groups as well as in the average for all groups.

It will be noted that the total number of patients responding is greatest in Groups I and II, less in Groups III and V, and least in Group IV. In all groups except in Group I, the total number responding among females is definitely smaller than among males.

The number of patients showing complete response, that is the response to both right- and left-sided pressure, is greatest in Groups I, II and III. In Groups IV and V the number showing complete response is greatly diminished. That is, in total response as in complete response, the females show a definitely smaller percentage response than males in each group as well as in the average for all groups.

In single-sided response, there is a greater percentage in Groups III, IV and V than in Groups I and II, and generally a greater percentage among females than among males. In all groups,

however, the number showing single-sided response is markedly smaller than those showing complete response, and the number responding on right-sided pressure is smaller than the number responding on left-sided pressure.

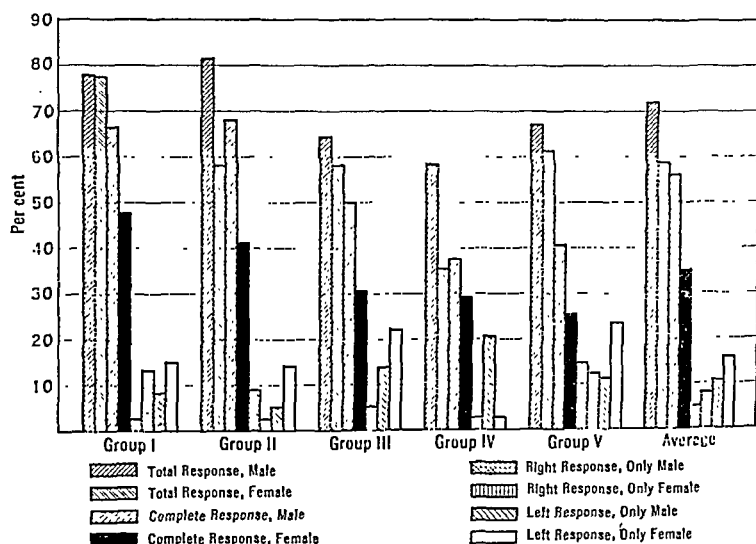


FIG. 1.—Percentage response to vagal stimulation. Total response includes all response. Complete response includes response to both, right and left stimulation in the same patient. Right response includes only response to right stimulation. Left response includes response only to left stimulation.

TABLE 1.—RESPONSE TO CAROTID SINUS PRESSURE AMONG MALES AND FEMALES.

Groups.	Total No. of cases.		Total not responding.		Total responding and percentage response.				Complete response and percentage.				Left response alone and percentage.				Right response alone and percentage.			
	Male.		Female.		Male.		Female.		Male.		Female.		Male.		Female.		Male.		Female.	
	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.
I	71	44	16	10	55	77.2	34	77.2	47	66.2	21	47.7	6	8.4	7	15.9	2	2.8	6	13.6
II	22	34	4	14	18	81.8	20	58.8	15	68.2	14	41.2	1	5.4	5	14.7	2	9.1	1	2.9
III	14	36	5	15	9	64.3	21	58.3	7	50.0	11	30.5	2	14.3	8	22.2	0	0.0	2	5.5
IV	24	34	10	22	14	58.3	12	35.2	9	37.5	10	29.4	5	20.8	1	2.9	0	0.0	1	2.9
V	27	39	9	15	18	66.6	24	61.5	11	40.7	10	25.6	3	11.1	9	23.1	4	14.8	5	12.8
Total	158	187	44	76	114	72.1	111	59.3	89	56.3	66	35.3	17	10.8	30	16.0	8	5.0	15	8.0

"Complete response" includes response to both right- and left-sided pressure.

To summarize, we find: (a) That the greatest number responding to carotid sinus pressure is in the arteriosclerotic and the hypertensive groups, although the other groups also responded in high percentages. The least response is shown in neurocirculatory

asthenia. (b) The response to both-sided pressure is greatest in arteriosclerotic, hypertensive and rheumatic heart disease, and much less in the non-cardiac groups where there seems to be a greater tendency toward response to one-sided pressure, especially left-sided. (c) Females show a much smaller incidence of response in all groups and one-sided response is more frequent in them than in males.

Degree of Slowing. The degree of slowing was determined by comparing the heart rate before and after sinus pressure was applied. The amount of pressure used was the maximum required in a given case to produce the maximum slowing. This amount varied with different patients. In many cases, very little pressure produced stoppage of the heart for as long as 2 to 7 seconds. In others, considerable pressure produced only 10 to 25 per cent slowing. In a few cases, instead of slowing, an acceleration of the heart was observed, probably due to pain or excitement incident to pressure, or perhaps to a cardio-accelerator reflex set up by the pressure.

In many cases the greatest amount of slowing occurred about 1 or 2 seconds after the maximum pressure was applied, and lasted as long as pressure was maintained. In all cases, except where the heart stopped, the rate obtained by pressure was multiplied by the time in seconds to arrive at the rate per minute. Thus, if the rate obtained was 4 beats in 6 seconds of pressure, the rate was considered to be 40 per minute. With a previous rate of 75 per minute, the slowing was taken to be about 53 per cent.

In some cases the slowing outlasted the pressure. This occurred in those cases which responded to a minimum amount of pressure. Here the pressure was at once discontinued for fear of untoward effects of heart stoppage, for in all these cases the heart stopped for 2 or more seconds. In most cases the heart rate would slow down on the first 5 or 6 seconds of pressure and would rise again on the continuation of such pressure.

The degree of slowing was divided into three grades—that of less than 25 per cent of the original rate, that of 25 to 75 per cent, and that with stoppage of the heart for more than 2 seconds. We shall consider these degrees of slowing as mild, moderate and marked, respectively.

Table 2 and Fig. 2 represent the various groups responding according to these degrees of slowing. It will be noticed that the percentage of patients showing mild degree of slowing is greatest in Groups IV and V and less in Groups, I, II and III. In all the groups the number of females responding in a mild degree invariably exceeds the number of males.

In all groups the predominant slowing is moderate in degree, and the number of females responding in that degree is also greater except in the non-cardiac groups where the number showing a marked degree of slowing is small, and the males respond predominantly in moderate degree.

In the cardiac groups, especially the arteriosclerotic and the rheumatic, there is a greater tendency toward a marked degree of slowing, and a greater number of males respond to such degree than females. In Group IV, the number showing a marked response is comparatively small. In Group V there seems to be a greater tendency for females to show such response. In the average for all groups, males show marked response in greater number than females.

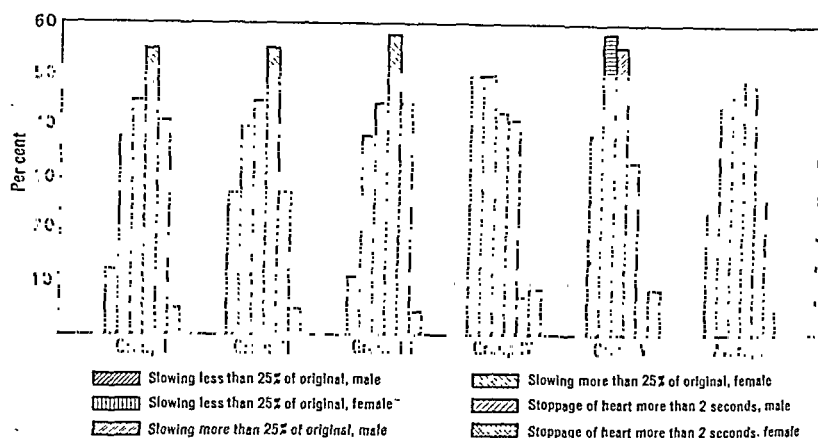


FIG. 2.—Degree of slowing.

TABLE 2.—DEGREE OF SLOWING IN THE VARIOUS GROUPS.

Groups.	Slowing, Less than 25% of original.				Slowing, More than 25% of original.				Heart stopped.			
	Male.		Female.		Male.		Female.		Male.		Female.	
	No. of cases.	Per cent.	No. of cases.	Per cent.	No. of cases.	Per cent.	No. of cases.	Per cent.	No. of cases.	Per cent.	No. of cases.	Per cent.
I	7	12.7	13	38.2	25	45.4	19	55.8	23	41.8	2	5.8
II	5	27.7	8	40.0	8	44.4	11	55.0	5	27.7	1	5.0
III	1	11.0	8	38.1	4	44.4	12	57.1	4	44.4	1	4.7
IV	7	50.0	6	50.0	6	42.8	5	41.6	1	7.1	1	8.3
V	7	38.8	14	58.3	10	55.5	8	33.3	1	5.5	2	8.3
Total	27	23.6	49	44.5	53	46.5	55	49.5	34	28.0	7	6.3

The percentage of slowing was arrived at by comparing the rate before with the rate after carotid sinus pressure was applied. The percentage number of cases showing the various degrees of slowing was calculated on the basis of the number of cases responding.

To summarize, we find: (a) That there is a greater tendency toward a mild or moderate degree of slowing in the non-cardiac groups of patients and moderate or marked in the cardiac groups. (b) Females show a greater tendency than males toward mild response, and lesser tendency toward marked response.

Discussion. It will be seen from the observations presented in this paper that reflex slowing of the heart produced by carotid sinus pressure occurs in a variety of conditions. The greatest incidence of response, especially of marked response to comparatively little pressure, occurs in arteriosclerosis and hypertension with evidence of severe myocardial damage, as well as in rheumatic heart disease. Its occurrence in other conditions, even if in a milder degree, and its absence in some very severe forms of cardiac disease call for broader explanations of this phenomenon than the mere presence of cardiac disease. Besides, the diminished response, both in incidence and degree, in neurocirculatory asthenia and in females cannot be explained merely on the bases of local disease. We must infer the existence of a vagotonic predisposition inherent in certain individuals, making them susceptible to reflex vagal activity. Although the Eppinger and Hess theory¹⁴ of vagotonic and sympathetotonic constitutions is applicable to a very limited number of cases, we cannot doubt the existence of a vagotonic predisposition without in most cases showing symptoms under ordinary circumstances, but exhibiting itself under adverse circumstances and caused by external stimulation. Judging from our findings, such vagotonic tendency is much smaller in females than in males and is also small in neurocirculatory asthenia. The actual existence in females and in neurocirculatory asthenia of a greater tendency toward sympathetic nerve response is evidenced by the frequent occurrence here of simple tachycardia and changing temperament.

We cannot doubt that local disease such as sclerosis at the carotid sinus, in the brain or in the heart affecting the various components of the reflex vagal arc may lower the threshold of irritability of that arc, thereby increasing the response. This is evident from the reports of the authors quoted in the preliminary remarks in this paper. It seems, however, that an inherent tendency toward vagal response is necessary to get the effects of carotid sinus pressure, even in those cases where such effects are expected to be present.

Summary and Conclusions. Carotid sinus pressure was carried out on a series of 345 cases, consisting of 158 males and 187 females. The cases were divided into the following five groups: (1) Arteriosclerotic heart disease; (2) hypertension and hypertensive heart disease; (3) rheumatic heart disease; (4) neurocirculatory asthenia, and (5) general constitutional disease with no cardiac abnormalities. There was a greater number of patients showing slowing, and the degree of slowing was much more marked in arteriosclerotic and hypertensive groups. The rheumatic heart disease and the general constitutional disease groups were next in number and degree of slowing. The neurocirculatory asthenia group showed the least number and lowest degree of slowing. In all groups, females showed a definitely milder grade of slowing than males, and the number responding was definitely smaller.

A possible explanation for the variation in response is that a vago-tonic predisposition is necessary for an effective response. This predisposition is greater in males, and less in neurocirculatory asthenia. Local disease, as sclerosis in the carotid sinus, vagal center or heart, greatly accentuates the reflex in the predisposed individual.

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CLINICAL OBSERVATIONS ON THE CAROTID SINUS REFLEX.

II. THE RESPONSE TO CAROTID SINUS PRESSURE AT VARIOUS AGES AND HEART RATES AND RHYTHMS.

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THIS paper deals with a further analysis of the series of cases reported in the preceding paper (I) as to the frequency of response to carotid sinus pressure at various ages, and under various heart rates and rhythms. The object of this study is to determine if vagal response is altered by age, and if a heart already under increased vagal influence such as in sinus bradycardia and sinus arrhythmia is more susceptible to reflex vagal stimulation than a heart under predominant sympathetic control such as in simple tachycardia.

Frequency of Response at Various Ages. All patients in the various groups were divided according to their ages into the following four subgroups: adolescents (5 to 20 years of age); adults (21 to 40); middle age (41 to 60); and old age (61 to 80).

We find in Table 1 and Chart I that in the average for all groups

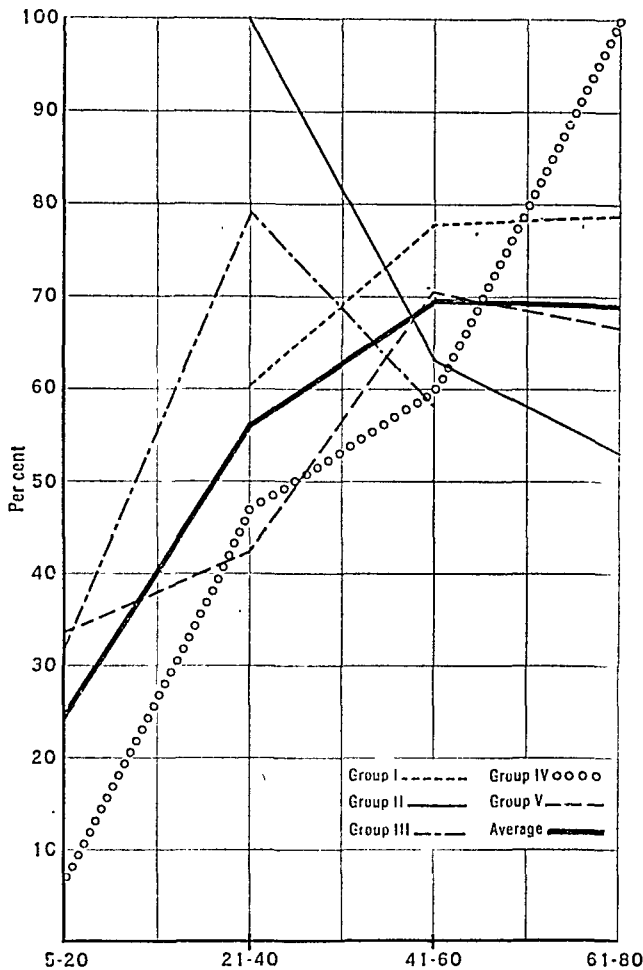


CHART I.—Percentage response to carotid sinus pressure at given ages. Ordinate represents percentage response. Abscissa represents age groups.

TABLE 1.—RESPONSES TO CAROTID SINUS PRESSURE, AT VARIOUS AGES AND IN THE VARIOUS GROUPS.

Groups.	Ages, 5 to 20 years.			Ages, 21 to 40 years.			Ages, 41 to 60 years.			Ages, 61 to 80 years.		
	No. re- spond- ing.	No. not re- spond- ing.	Per cent re- spond- ing.	No. re- spond- ing.	No. not re- spond- ing.	Per cent re- spond- ing.	No. re- spond- ing.	No. not re- spond- ing.	Per cent re- spond- ing.	No. re- spond- ing.	No. not re- spond- ing.	Per cent re- spond- ing.
I . . .	0	0	0.0	6	4	60.0	56	16	77.7	25	8	78.8
II . . .	0	0	0.0	3	0	100.0	24	14	63.2	8	7	53.3
III . . .	6	13	31.6	15	4	78.9	7	5	58.3	0	0	0.0
IV . . .	1	12	7.7	11	12	47.8	12	8	60.0	2	0	100.0
V . . .	2	4	33.3	14	19	42.4	17	7	70.8	2	1	66.6
Total av.	9	29	23.9	49	39	55.7	116	50	69.9	37	16	69.0

Group I, arteriosclerotic heart disease; Group II, hypertension and hypertensive heart disease; Group III, rheumatic heart disease; Group IV, neurocirculatory asthenia, and Group V, general constitutional disease.

as well as in the individual groups, the number of cases responding to carotid sinus pressure is small up to 20 years of age, and greatly increases between 21 and 40 years. The maximum response occurs between 41 and 60, after which age no definite further increase is noticed. The exceptions found may be accounted for by the insufficient number of cases observed. Thus, in the hypertensive group the curve shows a maximum rise between the ages of 21 and 40, but inasmuch as there were only 3 cases in that group at these ages, no conclusions can be drawn. Likewise, in the rheumatic heart

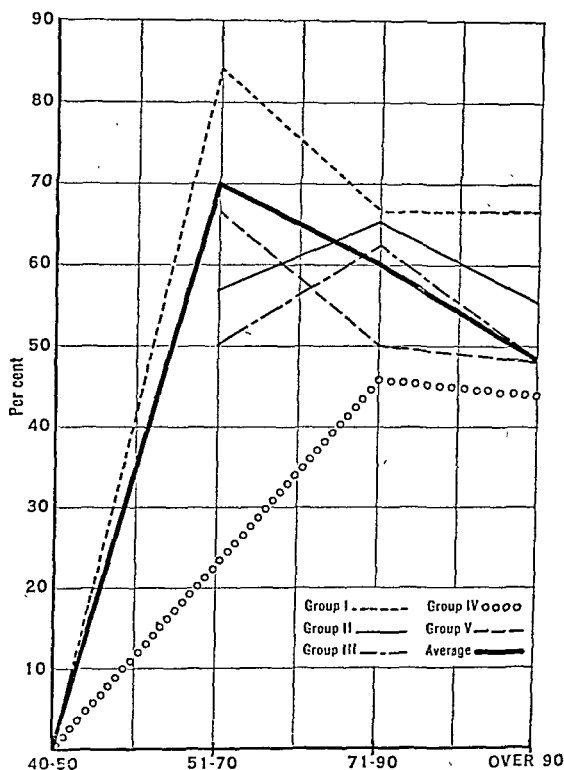


CHART II.—Percentage response to carotid sinus pressure with given heart rates. Ordinate represents percentage response. Abscissa represents rate of heart per minute.

disease group, the curve seems to show the highest peak between 21 and 40. Here there is a greater number of cases between those ages than at later ages, and again no definite conclusions can be drawn. In the neurocirculatory asthenia group, there seems to be a tendency toward a marked further rise after 61 years of age, but inasmuch as there are only 2 cases in this group above that age, no significance is to be attached to this rise.

In the arteriosclerotic and hypertensive groups, there were no cases younger than 20 years. In the rheumatic heart disease group,

there were no cases older than 60 years. The appropriate columns in those groups are therefore represented by zeros, and the respective curves start or end at ages where figures are available.

Frequency of Response With Various Heart Rates. In the determination of the frequency of response to carotid sinus pressure in individuals showing different heart rates, the various groups of patients were divided into the following four subgroups: (1) those showing very marked bradycardia (the rates being 40 to 50 beats per minute); (2) those with moderate bradycardia (rates varying between 51 and 70); (3) those with normal rates (between 71 to 90), and (4) those with tachycardia (rates of over 90 beats per minute).

It will be noticed (Table 2 and Chart II) that with heart rates of 50 or less beats per minute, no slowing was obtained by carotid sinus pressure. Although only 4 such cases have been observed and therefore no definite conclusions can be drawn, the absence of slowing in every case is nevertheless significant. With moderate bradycardias, on the other hand, the tendency for response appears to be maximum in the average, and in the arteriosclerotic and the various constitutional disease groups, while in the other groups it is slightly less than with normal heart rates. In view of the smaller number of cases in the moderate bradycardia group as compared with the group showing normal rates, the slightly diminished response here among the other disease groups is undoubtedly due to discrepancies in numbers. With rates of over 90, there is a decided drop in response in each group.

TABLE 2.—RESPONSE TO CAROTID SINUS PRESSURE AT VARIOUS HEART RATES IN THE VARIOUS DISEASE GROUPS.

Groups.	Rate, 40 to 50.			Rate, 51 to 70.			Rate, 71 to 90.			Rate, over 90.		
	No. re-spond-ing.	No. not re-spond-ing.	Per cent re-spond-ing.	No. re-spond-ing.	No. not re-spond-ing.	Per cent re-spond-ing.	No. re-spond-ing.	No. not re-spond-ing.	Per cent re-spond-ing.	No. re-spond-ing.	No. not re-spond-ing.	Per cent re-spond-ing.
I	0	2	0	25	5	83.3	36	17	67.0	20	10	66.6
II	0	0	0	4	3	57.0	27	14	65.8	5	4	55.5
III	0	0	0	3	3	50.0	17	10	62.9	8	9	47.2
IV	0	2	0	1	3	25.0	12	14	46.2	11	14	44.0
V	0	0	0	2	1	66.6	18	18	50.0	13	14	48.1
Total . . .	0	4	0	35	15	70.0	110	73	60.1	57	51	48.3

Group I, arteriosclerotic heart disease; Group II, hypertension and hypertensive heart disease; Group III, rheumatic heart disease; Group IV, neurocirculatory asthenia, and Group V, general constitutional disease.

Frequency of Response With Various Rhythms of the Heart. The entire series of cases presented three heart rhythms. Many cases in each rhythm showed premature contraction, but no separate

subdivision of such cases was made. There were 287 cases with regular sinus rhythm, 49 cases with definite sinus arrhythmia, and only 9 cases with auricular fibrillation. The preponderance in the number of cases of normal sinus rhythm over the other two rhythms, and especially over auricular fibrillation, makes comparison of response under the three rhythms not entirely reliable. Some deductions may, however, be made from the comparison.

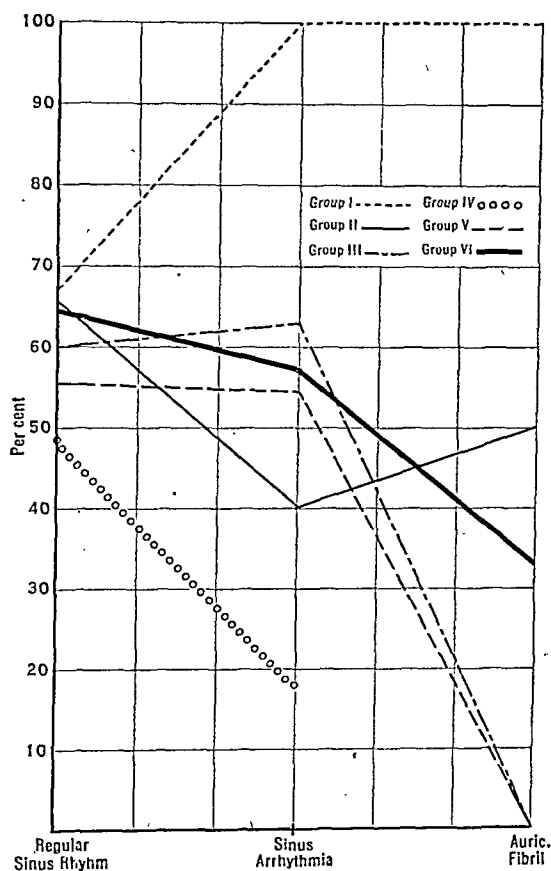


CHART III.—Percentage response to carotid sinus pressure in various rhythms. Ordinate represents percentage response. Abscissa represents rhythm.

We find (Table 3 and Chart III) that the curve of average response has its highest peak under regular sinus rhythm, a lower level under sinus arrhythmia, and lowest under auricular fibrillation. This applies with slight variation to all other curves except that of arteriosclerotic heart disease. Here there is a definitely greater proportional response with sinus arrhythmia and with auricular fibrillation. In both, all cases with arteriosclerotic heart disease responded. Although the number of such cases is small, complete response without

exception has some significance. In the hypertensive group, the curve has a tendency to rise in auricular fibrillation. As there were only 2 cases here, and only 1 responded, such rise has no significance. The lower response in sinus arrhythmia than in regular sinus rhythm in the average curve is undoubtedly due to the great discrepancy in a number of cases in the two rhythm groups.

TABLE 3.—RESPONSE TO CAROTID PRESSURE WITH VARIOUS RHYTHMS OF THE HEART IN THE VARIOUS DISEASE GROUPS.

Groups.	Regular sinus rhythm.			Sinus arrhythmia.			Auricular fibrillation.		
	No. re-spond-ing.	No. not re-spond-ing.	Per-cent-age re-sponse.	No. re-spond-ing.	No. not re-spond-ing.	Per-cent-age re-sponse.	No. re-spond-ing.	No. not re-spond-ing.	Per-cent-age re-sponse.
I	68	34	66.6	11	0	100.0	2	0	100.0
II	32	17	65.3	2	3	40.0	1	1	50.0
III	21	14	60.0	7	4	63.6	0	4	0.0
IV	23	24	48.9	2	9	18.1	0	0	0.0
V	30	24	55.5	6	5	54.5	0	1	0.0
Total	174	113	64.1	28	21	57.1	3	6	33.3

Group I, arteriosclerotic heart disease; Group II, hypertension and hypertensive heart disease; Group III, rheumatic heart disease; Group IV, neurocirculatory asthenia, and Group V, general constitutional disease.

Discussion. The essential findings recorded in this paper are: (1) That the carotid sinus reflex occurs infrequently in adolescence, increases in adult life, and reaches a fastigium in middle life. (2) That in marked bradycardia, no further reflex vagal slowing is obtained, and in tachycardia, the response is greatly diminished. The highest response occurs in the moderate bradycardia. (3) In sinus arrhythmia there is no appreciable difference in response over normal sinus rhythm except in arteriosclerotic heart disease where there is increased vagal response with this arrhythmia.

In my previous communication,¹ I stated that a logical explanation for the variation in response among certain groups of individuals and among the sexes is to be found in variation in the vagotonic predisposition. This predisposition seems to be less in females and in neurocirculatory asthenia. That local disease affecting the various components of the reflex vagal arc will lower the threshold of irritability of that arc, producing a heightened response, is evident. The fact that not all cases who show apparently similar disease exhibit the response seems to prove that the vagotonic predisposition is necessary in addition to a diseased state. In reviewing the literature on the oculocardiac reflex, we find that other authors seemed to have arrived at the same conclusion. Loeper and Mongeot² found an exaggerated oculocardiac reflex in hypervagotonic

and diminished in hypersympatheticotonic individuals. Gautrelet³ found the oculocardiac reflex to be exaggerated in hypervagotonic individuals.

The vagotonic tendency, judging from our additional observations presented in this paper, is small in adolescence, increases in adult life, and reaches a fastigium in middle life. Individuals who are already under extreme vagal tone, such as in marked bradycardia, do not seem to respond any further to increased vagal stimulation. The existence, however, of an evident moderate vagotonic state, as shown by moderate bradycardia, predisposes to increased vagal response. A physiologic limit of vagal tone apparently exists. In arriving at this conclusion, consideration must be given to the statement of Loeper and Mongeot⁴ that the oculocardiac reflex is preserved in bradycardias of nervous origin, but not of myocardial origin. They do not tell us, however, how differentiation of the two origins is made in cases of simple sinus bradycardia. Besides, our findings with the carotid sinus reflex seem to show that moderate simple sinus bradycardia accompanied by myocardial disease show a much greater tendency toward vagal response than the same forms of heart disease with a normal rate.

The arteriosclerotic heart disease group seems to show a definitely greater tendency toward increased vagal response, in cases of vagal hyperactivity, than in all other forms. This is evident from the rise in the curves of response here, in sinus bradycardia and more particularly in sinus arrhythmia. This phenomenon is hard to explain.

Summary and Conclusions. Observations on the carotid sinus reflex in a series of 345 cases showed that the response is small in adolescence, increases in adult life, and reaches a fastigium in middle life. The reflex was absent in cases of marked sinus bradycardia. In moderate bradycardia, on the other hand, the response is greatest. In tachycardia, it is greatly diminished. In arteriosclerotic heart disease, the general curve of response is higher than in the other groups, and those group with evident vagal activity, as shown by sinus bradycardia and sinus arrhythmia, responded most.

We may assume that a vagotonic predisposition is necessary to get a reflex vagal slowing of the heart by carotid sinus pressure. This predisposition progresses with age, reaching its maximum in middle life. A physiologic limit of this predisposition seems to exist, beyond which no further response is obtainable on stimulation. The constitutional state associated with arteriosclerosis heightens the vagotonic tendency.

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CLINICAL OBSERVATIONS ON THE CAROTID SINUS REFLEX.

III. THE RESPONSE TO CAROTID SINUS PRESSURE IN CASES
WITH AND WITHOUT PRECORDIAL PAIN.

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It is fairly well established that precordial pain is in many cases due to local asphyxiation of the heart muscle caused by local blood impoverishment. The greatest amount of asphyxiation occurs in coronary occlusion where the circulation to a local area is suddenly cut off. Hence pain is greatest and most prolonged under such conditions. Of some of the recent clinical and experimental evidence tending to substantiate this theory may be mentioned the work of Sutton and Lueth¹ and of Wood, Wolferth and Livezey.²

That the vagus nerve has a constricting effect on the coronary vessels was shown by Panim³ as long ago as 1858, and was repeatedly confirmed by numerous workers since, although apparently disproved by a few. Gilbert and Fenn⁴ in a recent experimental study found, like others before them, that digitalis has a vasoconstrictor effect upon the coronary vessels in some animals. It is also known that some cases of angina have followed the use of digitalis. They concluded that all cases of angina probably result from reflex vasoconstriction operating from various sources. It is caused by an overlable autonomic nervous system with lowered threshold. Greene⁵ found that efferent coronary vasoconstriction occurs through the vagus and vasodilation through the sympathetic. Normal reflex vasoconstriction is relatively weaker than vasodilation, and both correspond to the range of cardiac activity. In diseased hearts the reflex coronary vascular response is not in harmony with the reflex response of the heart itself. The result is that not enough coronary vasodilation occurs to ensure a sufficient blood supply to the heart during increased effort. Local asphyxiation of the heart muscle is the result and accounts for all cases of angina. This condition may result from vasoconstriction or failure of vasodilation.

It would seem that increased vagal tone with its efferent vasoconstriction effect on the coronary system may be at least partly responsible for angina in the presence of coronary sclerosis. We often find cases on the postmortem table with marked degrees of coronary sclerosis and even calcification without any history of angina during life. In these cases there must be a sufficient blood supply to the heart to prevent cardiac asphyxiation even in the presence of coronary sclerosis. The assumption may be made here that the added factor of heightened vagal tonicity of the coronary vessels is absent.

If this theory should be correct, a heightened carotid sinus reflex response which indicates increased vagal activity or lability should be a frequent accompaniment of precordial pain. I have accordingly analyzed the series of 345 cases reported in the two preceding articles^{6,7} with a view of determining the frequency of the carotid sinus reflex response in cases with and without precordial pain.

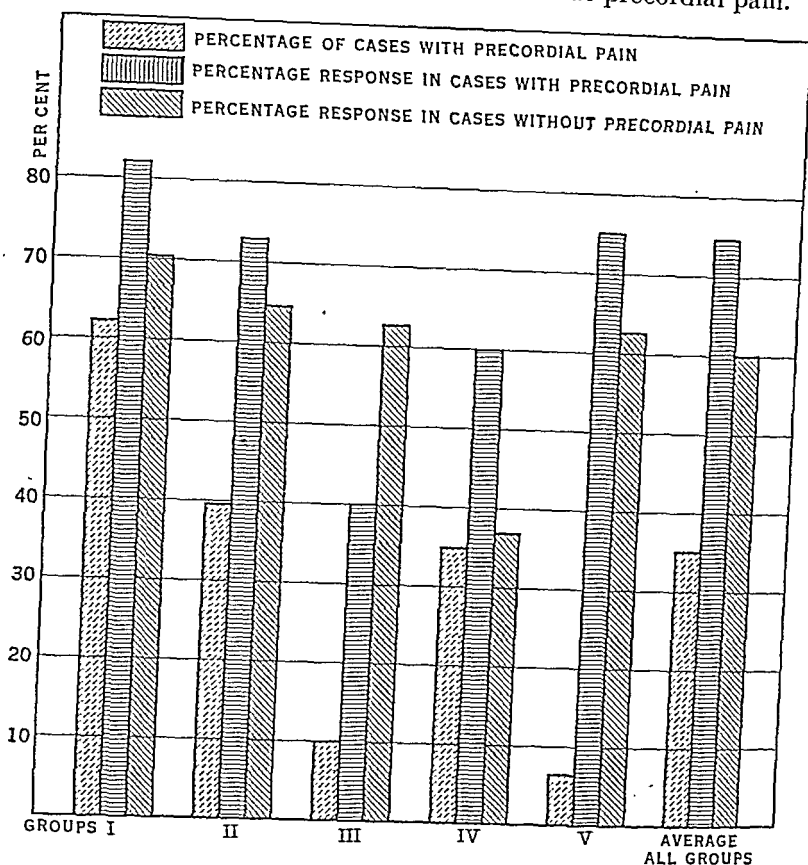


CHART I.—Percentage of cases with precordial pain and the carotid sinus reflex response in cases with and without pain.

These cases were divided according to the main diagnosis into the same five groups as in the first paper (see Table 1 of this paper). The preceding papers covered the frequency and the degree of response, in the various disease groups, among the sexes, at different ages and with various rates and rhythms of the heart. The present analysis covers the incidence of precordial pain in each group and the relative frequency of the carotid sinus reflex response in cases with and without such pain. Cases with precordial pain due to thoracic wall disease were classed under the subdivision of patients with no precordial pain.

The accompanying table and figure give a summary of the entire series of cases. We find that the percentage showing precordial

pain is greatest in the arteriosclerotic heart disease group, less in the hypertension group and least in the group with no cardiac disease, where it is almost negligible. The neurocirculatory asthenia group shows a comparatively high percentage of cases with precordial pain, while the rheumatic group shows the smallest percentage with such pain among the cardiac cases.

TABLE 1.—INCIDENCE OF PRECORDIAL PAIN AND THE CAROTID SINUS REFLEX RESPONSE IN CASES WITH AND WITHOUT PRECORDIAL PAIN.

Group.	Total number of patients.			Response of patients with precordial pain.			Response of patients without precordial pain.		
	With precordial pain.	Without precordial pain.	Percentage showing precordial pain.	Number responding.	Number not responding.	Percentage response.	Number responding.	Number not responding.	Percentage response.
I	71	44	61.7	58	13	81.7	31	13	70.4
II	22	34	39.2	16	6	72.7	22	12	64.7
III	5	45	10.0	2	3	40.0	28	17	62.2
IV	20	38	34.5	12	8	60.0	14	24	37.0
V	4	62	6.0	3	1	75.0	39	23	62.9
Total	122	223	35.3	91	31	74.6	134	89	60.0

Group I, arteriosclerotic heart disease; Group II, hypertension and hypertensive heart disease; Group III, rheumatic heart disease; Group IV, neurocirculatory asthenia, and Group V, general constitutional disease without any cardiac abnormalities. The total is the average for all the groups.

The carotid sinus reflex occurred with greatest frequency in cases with precordial pain in all groups except in the rheumatic heart disease group. The number of cases with precordial pain in this group, however, is too small to form a basis for definite conclusions. In neurocirculatory asthenia there was the greatest difference in response between those with and those without pain, as many as 23 per cent more of the cases with precordial pain responded.

Many cases that showed the greatest degree of vagal response in the arteriosclerotic group had no precordial pain. Some of these showed either effort or paroxysmal dyspnea, asthenia or more or less congestive failure as evidence of cardiac disease. Some showed no evident symptoms but the electrocardiogram was distinctly abnormal. In the group of neurocirculatory asthenia, on the other hand, the degree of response was somewhat greater in cases presenting precordial pain.

In the group with no heart disease, there were only 4 cases that showed some precordial pain and of these 3 (75 per cent) showed response. This number of cases, however, is too small for comparison with the greater number of cases in this group who had no precordial pain.

Slight precordial pain was produced by carotid sinus pressure

in very few instances where no pain was present at the time such pressure was applied. No accentuation of pain occurred if pain was present.

In the majority of cases no untoward effects of carotid sinus pressure were noticed. Several cases where the heart slowed to any marked extent complained of dizziness. Some developed a sensation of fainting, and two developed momentary unconsciousness. In a few cases there was some respiratory embarrassment, and some developed a mild coughing spell during the entire period of carotid sinus pressure.

Comment. It would seem that precordial pain may be due in some cases to increased vagal activity. The number of such cases is the difference in the number responding to carotid sinus pressure among those with and those without pain. In the arteriosclerotic group it is about 11.3 per cent, in the hypertensive group 8 per cent, in neurocirculatory asthenia it is highest, being about 23 per cent, while in the non-cardiac group it is 12.1 per cent.

Although these percentages are small they indicate that lability of the autonomic nervous system, especially that of the vagal portion, is in some way connected with the production of precordial pain at least in some instances. The work of the authors previously mentioned point to vasoconstriction of the coronary vessels with the resultant local asphyxia as the possible mode of production of pain in these cases. The number of cases in which this mechanism of pain production is operative is probably equal to that number of cases that will show the anginal syndrome under digitalis, being a vagotropic drug.

That not all cases with increased vagal tone show precordial pain, and that not all painful cases have an increased vagal tone would indicate that additional factors are concerned in the pathogenesis of precordial pain.

Summary. In a series of 345 cases it was found that the carotid sinus reflex occurs more often among patients with than without precordial pain. The greatest difference occurs in neurocirculatory asthenia. Many cases with a high degree of response had no pain, and very seldom was pain elicited or accentuated in any case by carotid sinus pressure.

The findings indicate that increased vagal activity with the resultant coronary vasoconstriction and cardiac anemia may be the cause of angina in some cases.

I am indebted to Dr. Robert H. Halsey for his valuable criticism and suggestions in the preparation of this and the preceding papers.

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REVIEWS.

CALCIUM METABOLISM AND CALCIUM THERAPY. By ABRAHAM CANTAROW, M.D., Instructor in Medicine, Jefferson Medical College, etc. With a Foreword by HOBART AMORY HARE, B.Sc., M.D., LL.D., late Professor of Therapeutics, Materia Medica and Diagnosis in the Jefferson Medical College. Pp. 252. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1933. Price, \$2.50.

THE rapid developments in the study of calcium metabolism, both diagnostically and therapeutically, make this edition highly desirable even after the short space of two years. The chief changes from the first edition are on "the altered conception of the relationship between the parathyroid hormone and vitamin D; the relation of the calcium and phosphorus intake to the effects of vitamin D and the parathyroid hormone; the significance of phosphatases in the mechanism of ossification and in bone diseases; dental caries; the influence of calcium upon the pharmacological action of various drugs; the *in vivo* diffusibility of calcium in nephritis with uremia and in parathyroprivic tetany; the nature of parathyroid hormone action."

F. K.

EXPERIMENTAL PHARMACOLOGY AND TOXICOLOGY. By HENRY G. BARBOUR, A.B., M.D., Yale University, New Haven. Pp. 141; 14 illustrations. Philadelphia: Lea & Febiger, 1932. Price, \$2.75.

THIS book outlines a laboratory course in pharmacology for medical students. Outstanding chemical and physiological properties of important drugs are illustrated by simple, direct experiments which have proved successful in the author's extensive experience. The material is useful to the teacher of pharmacology, but it is too elementary to be of much value to the toxicologist, and there is too little coördination with physiology for the clinician seeking new information concerning drug actions.

J. R.

ESSENTIALS OF PEDIATRIC NURSING. By RUTH ALICE PERKINS, R.N., B.S., Graduate of Children's Memorial School of Nursing, etc. Pp. 467; 55 engravings and 6 full page colored plates. Second edition, revised and enlarged. Philadelphia: F. A. Davis Company, 1932.

THE book is wide in its scope, laying particular stress upon the important subject of preventive pediatrics. It endeavors to instruct the nurse in the phases of work encountered in the home, the health center, the outpatient clinic as well as in the medical and surgical wards of the hospital. An excellent section is that devoted to the psychology and mental hygiene of the child, and to the consideration of the child as a personality as well as an example of a disease. The inclusion of valuable bibliographic material makes for great usefulness. The description of some of the medical diseases might benefit by fuller consideration and by inclusion of some of the physiologic background of these conditions. However, all information essential to the nurse is well covered. The sections on communicable diseases and aseptic nursing technique are splendid and well worth consideration by the physician. This book may be recommended as broad in vision, accurate in information, practical, and elegantly set up and illustrated.

J. S.

A TEXTBOOK OF PATHOLOGY. By W. G. MACCALLUM, Professor of Pathology and Bacteriology, The Johns Hopkins University, Baltimore. Pp. 1212; 652 illustrations. Fifth edition, thoroughly revised. Philadelphia: W. B. Saunders Company, 1932. Price, \$10.00.

SINCE the first appearance of this book in 1916, the years 1923, 1927, 1930 are the only ones in which a new printing or new edition has not appeared. An enviable record, indeed, that suggests obvious comparisons with that other great Hopkins textbook, Osler's *Practice*. In this latest revision the sections on tuberculosis, syphilis, nephritis, endocarditis and endocrine disorders have been subject to the most change. Among the new material included are items on arteriolosclerosis, congenital heart disease, tularemia, postvaccinal encephalitis, agranulocytosis, ligneous thyroiditis, otitis fibrosa and a chapter on disorders of lipid metabolism. Many of the drawn illustrations—always an excellent feature of the book—have been replaced by photographs, a desirable substitution if, as here, the high standard can be maintained. The lung photographs (Figs. 333 to 347) are especially praiseworthy.

E. K.

CLINICAL GYNECOLOGY. By C. JEFF MILLER, M.D., Professor of Gynecology, Tulane University School of Medicine; Chief of the Department of Gynecology of Touro Infirmary, etc. Pp. 560; 134 illustrations. St. Louis: The C. V. Mosby Company, 1932. Price, \$10.00.

THIS book is a companion volume to "An Introduction to Gynecology" (1931), in which were discussed the fundamentals of gynecology with little or no reference to therapy. In the present volume the author comprehensively sets forth his views as to medical therapy and operative treatment for gynecologic diseases. His long experience permits him to speak authoritatively and his individual preference for particular measures are strongly indicated. He has interpolated the expressed ideas of other authors and operators; these are frequently and copiously quoted and discussed, and at times disagreed with in a friendly manner. This unusual manner of presentation of the literature adds much to the interest and ease of reading the book.

The teaching in the book is modern and rational and where a personal choice is emphasized it is always soundly conservative. There is no doubt but that this volume devoted solely to therapy will be largely and warmly received.

P. W.

THE SPUTUM. By RANDALL CLIFFORD, M.D., Associate in Medicine, Peter Bent Brigham Hospital; Assistant in Medicine, Harvard Medical School. Pp. 167; 21 illustrations, 7 colored plates. New York: The Macmillan Company, 1932. Price, \$4.00.

THIS volume is well printed on good paper in clear readable type and is suitably bound for hard use. It is divided into 11 chapters, each followed by a sufficiently comprehensive bibliography. There is a 12-page index. The 11 chapters are divided into 4 sections, including general considerations, macroscopic examination, microscopic examination and the sputum in some of the more common diseases of the bronchi and lungs. The chapters dealing with the origin and significance of the various types of sputum are fairly complete. The only method given for the Gram staining of bacteria is not in very general use, but is fairly simple and probably as satisfactory as any. It would have been helpful if some space had been devoted to methods of cell staining. The importance recently ascribed to pulmonary spiro-

cheto-sis would seem to require more attention than the author has devoted to it. The book is well written and the material well chosen. It will be of value both to the clinician and the laboratory worker.

F. L., Jr.

PRACTICAL OBSTETRICS. By P. BROOKE BLAND, M.D., Professor of Obstetrics, Jefferson Medical College; Chief Obstetrician, Jefferson Medical College Hospital. Assisted by THADDEUS L. MONTGOMERY, M.D., Associate in Obstetrics, Jefferson Medical College. Pp. 730; 516 illustrations, including 21 colored plates. Philadelphia: F. A. Davis Company, 1932. Price, \$8.00.

THIS medium-sized volume developed from the author's teaching gives a concise presentation of modern conservative obstetrics. The chapters are arranged logically to carry the students through the entire subject. For the practitioner the advice given as to treatment is rational and always conservative.

The newer ideas of the physiology of the reproductive organs are presented in an interesting manner as they relate to diagnosis and parturition. In the discussion of normal pregnancy one may question the advisability of making a vaginal examination on each return visit; on the other hand, the advice about unnecessary vaginal examinations late in pregnancy and in labor is good. For normal labor the modified Garden of Eden plan with constant alertness is advocated. For the aftercoming head the forceps of Piper is the preferred. Potter's version is beautifully illustrated, though indications for its use are lacking. For placenta previa prompt Cesarean section is urged, with transfusions if necessary.

Under obstetric analgesia-anesthesia the need for special nursing care, or crib beds, for the partly unconscious patient is not stressed. Section on the newborn is well developed. Some of the methods for resuscitation of the newborn seem obsolete. Stander's classification of the toxemias is comprehensively discussed. Fay and Arnold's dehydration treatment is described but not evaluated. The quick termination of pregnancy in progressive toxemias by abdominal hysterectomy with local anesthesia is not more than mentioned, in contrast to the recommended bougie induction of labor. In posterior occiput dystocias manual rotation and forceps are preferred; expectancy is recommended in breech cases. On the moot point of lumbar puncture in intracranial hemorrhage in the newborn, repeated taps are recommended. There is a section on obstetric jurisprudence, quite germane to the subject and seldom seen in textbooks. The appendix on referred reading is a noteworthy addition.

The book is well adapted to students for the definite and clear presentation given, the succinct paragraphs on pathology, complications and treatment will appeal to the general practitioner, as will also the generally conservative tone of the book.

P. W.

PHYSICAL CHEMISTRY FOR STUDENTS OF BIOLOGY AND MEDICINE. By DAVID INGERSOLL HITCHCOCK, Ph.D., Associate Professor of Physiology in the Yale University School of Medicine. Pp. 182; 26 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, \$2.75.

THIS short text in physical chemistry covers only those topics that are important for students in physiology and medicine. These include such fundamental subjects as the gas laws, the laws of solution and the colloidal state, followed by chapters of more immediate physiologic interest on equilibria in blood, enzyme action and oxidation-reduction potentials.

The latter chapters will be useful to many investigators in related fields because of the recent rapid growth of these subjects. The present Reviewer has found them presented in a clear and readable manner. For the student there are lists of questions at the end of each chapter and a bibliography of original papers and texts for further reading. A good feature is brief biographical sketches in footnotes of important physical chemists. Use of this book does not require knowledge of higher mathematics.

M. McC.

CHILDREN'S TONSILS IN OR OUT. By ALBERT D. KAISER, M.D., Associate Professor of Pediatrics, University of Rochester Medical School. Pp. 307; 25 illustrations. Philadelphia: J. B. Lippincott Company, 1932. Price, \$5.00.

THE author's carefully conducted researches in this field qualify him eminently for writing a book of this kind. It represents the results of a 10 year's study involving nearly 5000 children, and planned particularly to secure data on the value of tonsil and adenoid operations. The need for such a book is apparent to the practising physician, who, with his colleague the laryngologist, is often perplexed as to whether operation shall or shall not be performed. Controlling his observations by comparing groups of children with similar conditions, half of whom had had the advised operation, and half of whom did not, the author has considered the relations of tonsils and adenoids to common colds, tonsillitis, laryngitis, cervical adenitis, otitis, sinusitis, bronchitis as well as many general conditions such as scarlet fever, rheumatic disease, nephritis and pyelitis. There are chapters on the history of tonsillectomy, the anatomy, physiology and bacteriology of the tonsils, the symptoms of pathologic tonsils and adenoids, the hazards of tonsillectomy, on incomplete tonsillectomy, on radiation therapy and on electrosurgery of the tonsils. The final chapter summarizes the evidence and on that basis presents the indications for and the contraindications to tonsillectomy. This book should find a welcome reception by those concerned with the health of children. It is attractively printed in good-sized type on a dull-finished paper.

J. S.

ORAL SPIROCHETES AND RELATED ORGANISMS IN FUSOSPIROCHETAL DISEASE. By DAVID T. SMITH, A.B., M.D., Associate Professor of Medicine Duke University School of Medicine, Durham, N. C. Pp. 243; 53 illustrations. Baltimore: The Williams & Wilkins Company, 1932. Price, \$4.50.

THIS valuable monograph on the fusospirochetal infections of man is not of interest to the stomatologist alone as the title might indicate at first glance. Spirochetal bronchitis, bronchiectasis, lung abscess and pulmonary gangrene are dealt with clearly from a clinical and laboratory point of view, with the statement that spirochetes are probably the most frequent of serious pulmonary invaders in chronic non-tuberculous processes. The possible relation of fusospirochetal infection to agranulocytic angina, infectious mononucleosis, and pseudoleukemia is briefly discussed. The author suggests a possible rôle for these organisms in Ludwig's angina, amebic dysentery, and focal infection from oral sources. Fusospirochetal dysentery, appendicitis, laryngitis, tropical ulcer and genital infections are given separate chapter headings. Considerable fault can be found with the chapter on pyorrhea alveolaris. The morphology and biology of the oral spirochetes and associated bacteria are well discussed. It seems unfor-

tunate that the oral protozoa were not described. Experimental and clinical evidence is presented that the following four organisms must be in symbiotic relationship to produce most clinical pictures; a spirochete, a fusiform bacillus, a vibrio, and a streptococcus. Cultural evidence indicates that fusiform bacilli are dissociated forms of spirochetes. The bibliography lists 522 references.

H. H.

AMERICAN AND CANADIAN HOSPITALS. A Reference Book edited by JAMES CLARK FIFIELD, with the coöperation of the American Hospital Association. Pp. 1560; 1 colored illustration. Minneapolis: Midwest Publishers Company, 1933. Price, \$10.00.

THIS highly useful book, fostered by the American Hospital Association, contains short accounts of the history and present status and statistics of all the hospitals of the United States and Canada. As far as we have been able to test the matter, its content is accurate, inclusive, pertinent and up to date. As a work of reference it should be invaluable to those seeking information of this kind. A 58-page Appendix contains considerable information about institutions concerned with hospital work.

E. K.

STREPTOCOCCI IN RELATION TO MAN IN HEALTH AND DISEASE. By ANNA W. WILLIAMS, M.D., First Assistant Director, Bureau of Laboratories, Department of Health, City of New York. Pp. 260; 7 plates, 1 illustration and 19 tables. Baltimore: The Williams & Wilkins Company, 1932. Price, \$5.00.

DR. WILLIAMS is to be congratulated upon the production of this very readable monograph. It is complete without being cumbersome. To those engaged in the general or special practice of medicine it can be wholeheartedly recommended as a thorough review of a subject which is of great practical importance. As a conservative exposition of the progress which has been made in a field where much loose thinking has from time to time been exploited, it should be of great service in the avoidance of faddism. Particularly valuable is the conservative attitude toward serum and vaccine therapy. The research worker, who is conversant with the present need for progress in the knowledge of streptococci and streptococcal disease, will welcome, from one of the leading investigators in the field, this summary of past and present accomplishment; although he may feel some disinclination to agree with the identification of endotoxin with specific agglutinin. To him, many problems for future inquiry will be suggested by the merciless exposition of existent gaps in our knowledge.

It is unfortunate that a work of such high quality should be marred by numerous typographical errors of omission and commission.

C. H.

MODERN ALCHEMY. By WILLIAM ALBERT NOYES, University of Illinois, and W. ALBERT NOYES, JR., Brown University. Pp. 207; 17 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, \$3.00.

THE Preface of this book contains the following: "For more than a thousand years alchemists sought in vain for the Philosopher's Stone, which should transmute base metals into gold and for an Elixir of Life, which should give eternal youth. The quest was finally abandoned as hopeless, but the transmutation of elements has been observed in recent

times and many ways of healing disease and prolonging life have been found. The vicissitudes of the search for transmutation and for healing principles are typical of the progress of science and have been taken as the groundwork of this book. In the first chapter, there is a superficial survey of the various branches of science and an attempt is made to discover their common characteristics. This is followed by an outline of modern ideas about the constitution of matter, given as an illustration of the scientific method in dealing with one of the most fundamental problems engaging the attention of scientific men and as a basis for the discussion of valence."

There are thus discussed the methods of science, atomic structure, the transmutation of the elements, the philosopher's stone, valence, the effect of various radiations on chemical systems, new elements and new uses for old ones, the elixir of life.

The authors are well known Professors of Chemistry who have presented in readable form subjects of major importance to the progress of medicine.

B. L.

GROWTH. By the LATE JAMES LORRAIN SMITH, M.D., LL.D., D.Sc., F.R.S., Professor of Pathology, University of Edinburgh. Edited by J. S. HALDANE, C.H., M.D., F.R.S. Pp. 131; 1 illustration. Edinburgh: Oliver & Boyd, 1932. Price, 6/- net.

AN understanding of "Growth," the creative principle of the body would go far toward supplying an understanding of life itself, to say nothing of such important diseases as carcinoma and sarcoma. The present small and inexpensive but attractive volume gives Lorrain Smith's thoughts on these subjects. An introduction and 14 chapters had been practically finished before his death. The imperfect sketches of other chapters have been omitted and a supplementary chapter added by the author. Growth and size as expressed by increase in number of cells and occasionally in size of cells, the difference of fish growth from mammalian growth, why repair stops when the original size is restored, why liver—though existing in amounts more than needed—"is rigidly restored to the full amount" after partial destruction—such topics indicate the interest that one expects to derive from perusal of this thoughtful effort.

E. K.

ELEMENTS OF ELECTROCARDIOGRAPHIC INTERPRETATION. By LOUIS N. KATZ, A.M., M.D., Physiologist and Director of Cardiovascular Research, The Michael Reese Hospital, Chicago; Assistant Professor of Physiology, The University of Chicago, and VICTOR JOHNSON, Ph.D., Instructor in Physiology, The University of Chicago. Pp. 39; 38 plates. Chicago: The University of Chicago Press, 1932. Price, \$1.00.

THIRTY-EIGHT excellent electrocardiograms (one to a page), illustrating 36 different deviations from the normal, comprise the body of this useful booklet. With the exception of a short preface, a table of characteristics of the normal electrocardiographic cycle and a very practical appendix ("Procedure in reading an electrocardiogram"), the rest of the text consists of copious legends to each figure. The book obviously and admittedly omits consideration of the *raison d'être* of the electrocardiogram and of all but the electrocardiographic phases of cardiology. However, as an auxiliary to more comprehensive efforts it covers the field indicated in its title so excellently, that it may be enthusiastically recommended to the non-specializing internist and the beginning student of cardiac physiology for whom it has been prepared.

E. K.

ELEKTROKARDIOGRAPHIE FÜR DIE AERZTLICHE PRAXIS. Vol. 14 of Medizinische Praxis, Sammlung für Aerztliche Fortbildung. Herausgegeben von L. R. Grote, A. Fromme, K. Warnekros. By PROF. DR. ERICH BODEN, Direktor der Med. Poliklinik der Med. Akademie, Düsseldorf. Pp. 161; 91 illustrations (some colored). Leipzig: Theodor Steinkopff, 1932. Paper, Rm. 12; Cloth, Rm. 13.50.

Like several books on clinical electrocardiography in English that have been reviewed in these columns, these 14 lectures cover first the underlying principles of electrocardiography in health and disease (5 lectures), and next in more detail the practical applications, with inclusion of typical case reports (9 lectures). Especially praiseworthy are the diagrammatic drawings of the opened heart, accompanying the appropriate electrocardiograms. Bundle branch and arborization block are considered in the lecture on myocardial disease and in the former the older nomenclature is retained.
E. K.

BOOKS RECEIVED.

NEW BOOKS.

Dietetics for the Clinician. By MILTON ARLANDEN BRIDGES, B.S., M.D., F.A.C.P., Associate in Medicine at the New York Post-Graduate Medical School, Columbia University, in Collaboration with RUTH LOTHROP GALLUP, Dietitian. Foreword by HERMAN O. MOSENTHAL, A.B., M.D., Director of Medicine at the New York Post-Graduate Medical School, Columbia University. Pp. 666; 31 tables. Philadelphia: Lea & Febiger, 1933. Price, \$6.50.

Light Therapy. By FRANK HAMMOND KRUSEN, M.D., Director of the Department of Physical Medicine, Temple University School of Medicine, Philadelphia. Foreword by JOHN A. KOLMER, M.D., Dr. P.H., D.Sc., LL.D., Professor of Medicine, Temple University School of Medicine. Pp. 196; 33 illustrations. New York: Paul B. Hoeber, Inc., 1933. Price, \$3.50.

Intracranial Tumors. By PERCIVAL BAILEY, Professor of Surgery, University of Chicago. Pp. 475; 157 illustrations. Springfield, Ill.: Charles C Thomas, 1933. Price, \$6.00.

Operative Surgery. By ALEXANDER MILES, M.D., LL.D., F.R.C.S. (Ed.), Consulting Surgeon, Royal Infirmary, Edinburgh, and D. P. D. WILKIE, M.D., F.R.C.S. (Ed. and Eng.), Professor of Surgery, University of Edinburgh. Pp. 590; 321 illustrations. New York: Oxford University Press, 1933. Price, \$5.25.

Practical Hematological Diagnosis. By O. H. PERRY PEPPER, M.D., Professor of Clinical Medicine, University of Pennsylvania; Assistant Chief of the Medical Clinic, Hospital of the University of Pennsylvania, and DAVID L. FARLEY, M.D., Physician to the Pennsylvania Hospital, Philadelphia, and to the Cooper Hospital, Camden, N. J.; Associate in Medicine at the University of Pennsylvania. Pp. 562; 3 plates of colored illustrations. Philadelphia: W. B. Saunders Company, 1933. Price, \$6.00.

- The Nervous Child at School.* By HECTOR CHARLES CAMERON, M.A., M.D. (CANTAB.), F.R.C.P. (LOND.), Physician in Charge of the Children's Department, Guy's Hospital. Pp. 160. New York: Oxford University Press, 1933. Price, \$1.50.
- Proceedings of Meetings of the New York Pathological Society, 1932.* Pp. 53; 6 illustrations.
- Binocular Vision and the Modern Treatment of Squint.* By MARGARET DOBSON, M.D. (LOND.), Ophthalmic Surgeon to the New Sussex Hospital for Women and Children, Brighton; Oculist in Charge of the Kilburn (L.C.C.) Eye Clinic. Pp. 107; 32 illustrations. New York: Oxford University Press, 1933. Price, \$2.75.
- The Physio-chemical Theory of the Process of the Internal Defence of Animals.* (A Preliminary Report.) By DAVID SATY ANAND, M.B., B.S., House Physician, Infectious Diseases Hospital, Lahore, India. Pp. 91. Anarkali, Lahore: P. R. B. S. Press, 1933.
- Surgical Anatomy.* By C. LATIMER CALLANDER, A.B., M.D., F.A.C.S., Assistant Clinical Professor of Surgery and Topographic Anatomy, University of California Medical School; Associate Visiting Surgeon to the San Francisco Hospital. With a foreword by DEAN LEWIS, M.D., Sc.D., LL.D., F.A.C.S. Pp. 1115; 1280 illustrations. Philadelphia: W. B. Saunders Company, 1933. Price \$12.50.
- Operative Surgery, Vol. VII.* The Newest Operations, General Index to Complete Work, Vols. I-VII. By WARREN STONE BICKHAM, M.D., and PHAR.M. (TULANE), M.D. (COLUMBIA), F.A.C.S., Junior Surgeon to Touro Hospital, New Orleans; Fellow of the New York Academy of Medicine, etc., and CALVIN MASON SMYTH, JR., B.S., M.D., F.A.C.S., Assistant Professor of Surgery, Graduate School of Medicine, University of Pennsylvania; Surgeon-in-Chief, Methodist Episcopal Hospital; Visiting Surgeon, Abington Memorial Hospital. Pp. 849; 765 illustrations. Philadelphia: W. B. Saunders Company, 1933. Price, \$10.00.
- The Surgical Clinics of North America. Vol. 13, No. 2* (New York Number, April, 1933). Pp. 274; 56 illustrations. Philadelphia: W. B. Saunders Company, 1933.
- A System of Bacteriology in Relation to Medicine, Vol. VI. Immunity.* By various authors. Pp. 537; illustrated with charts and tables. London: Medical Research Council, 1931. Price, £1.1.9 for this volume; for the set £8.14.9. Obtainable in the United States at British Library of Information, 5 E. 45th Street, New York.
- Roentgenographic Studies of the Urinary System.* By WILLIAM E. LOWER, M.D., F.A.C.S., Chief of Department of Urology, Cleveland Clinic; Former Associate Professor of Genitourinary Surgery, Western Reserve University; Surgeon to Cleveland Clinic Hospital, and BERNARD H. NICHOLS, M.D., F.A.C.R., Chief of Department of Roentgenology, Cleveland Clinic. Pp. 812; 812 illustrations. St. Louis: The C. V. Mosby Company, 1933. Price, \$16.00.
- The Physiological Effects of Radiant Energy.* By HENRY LAURENS, Ph.D., Professor of Physiology in the Tulane University School of Medicine. Pp. 610; 104 illustrations. New York: The Chemical Catalog Company, Inc., 1933. Price, \$6.00.
- Manuscripta Medica.* A Descriptive Catalogue of the Manuscripts in the Library of the Medical Society of London. By WARREN R. DAWSON, F.R.S.E., F.R.S.L., F.S.A. (SCOT.), Fellow of the Royal Society of Medicine (Vice-President, Section of History); Honorary Research Assistant, Department of the History of Medicine, University College, London; Honorary Librarian of Lloyd's. Pp. 140. London: John Bale Sons & Danielsson, Ltd., 1932. Price, 15s.

The International Medical Annual, Fifty-first Year, 1933. A Year Book of Treatment and Practitioner's Index. By various contributors. Edited by CAREY F. COOMBS, M.D., F.R.C.P. (the late), and A. RENDLE SHORT, M.D., B.S., B.Sc., F.R.C.S. Pp. 572; 98 illustrations and 61 plates, some colored. Baltimore: William Wood & Co., 1933. Price, \$6.00.

It maintains its high grade of reporting current advances, and the illustrations are especially praiseworthy.

Kreislaufstörungen und Pathologische Histologie. By PROFESSOR DR. MARTIN NORDMANN, Privatdozent für allgemeine Pathologie und spezielle pathologische Anatomie an der Universität Tübingen. Band IV. Ergebnisse der Kreislafforschung. Monographien aus dem Gebiete Beschreibender, Experimenteller und Klinischer Kreislafforschung. Herausgegeben von DR. MED. BRUNO KISCH, Ord. Professor der Physiologie an der Universität Köln. Pp. 174; 14 illustrations. Leipzig: Theodor Steinkopff, 1933. Price: Paper, Rm. 13.50; Cloth, Rm. 15.00.

Sécrétion Interne et Régénérescence. By DR. N. E. ISCHLONDSKY. Pp. 336; 72 illustrations. Paris: G. Doin & Cie., 1933. Price, 90 fr.

Lymphatics, Lymph and Tissue Fluid. By CECIL K. DRINKER, B.S., M.D., Professor of Physiology, Harvard School of Public Health, and MADELEINE E. FIELD, A.B., PH.D., Instructor in Physiology, Harvard School of Public Health. Pp. 254; 11 illustrations and various tables. Baltimore: The Williams & Wilkins Company, 1933. Price, \$3.00.

History of Urology. In Two Volumes. Prepared under the Auspices of the American Urological Association. Editorial Committee: EDGAR G. BALLENGER, WILLIAM A. FRONTZ, HOMER G. HAMER, BRANSFORD LEWIS, Chairman. Pp. 746; 49 illustrations. Baltimore: The Williams & Wilkins Company, 1933. Price, \$8.00 set.

NEW EDITIONS.

Peptic Ulcer. By JACOB BUCKSTEIN, M.D., Instructor in Gastrointestine Roentgenology, Cornell University Medical College; Associate Attending Gastroenterologist, Sydenham Hospital, etc. Vol. 10 of Annals of Roentgenology, Edited by JAMES T. CASE, M.D., Professor of Radiology, Northwestern University Medical School. Pp. 417; 411 illustrations. Second edition revised and enlarged. New York: Paul B. Hoeber, Inc., 1933. Price, \$12.00.

A Companion to Manuals of Practical Anatomy. By E. B. JAMIESON, M.D., Senior Demonstrator and Lecturer on Anatomy, University of Edinburgh. Pp. 654. Third edition. New York: Oxford University Press, 1932. Price, \$5.00.

Clinical Aspects of the Electrocardiogram. By HAROLD E. B. PARDEE, M.D., Assistant Professor of Clinical Medicine, Cornell University Medical College; Associate Attending Physician, New York Hospital; Consulting Cardiologist, Lying-in Hospital and Woman's Hospital, New York City. Pp. 295; 74 illustrations. Third edition, revised. New York: Paul B. Hoeber, Inc., 1933. Price, \$5.50.

Surgical Operations. A Textbook for Students and Nurses. By E. W. HEY GROVES, M.D., B. Sc., M.S., F.R.C.S., Consulting Surgeon, Bristol General Hospital; Emeritus Professor of Surgery, University of Bristol, etc. Pp. 263; 204 text illustrations and 37-page Appendix of illustrations of instruments. Third edition. New York: Oxford University Press, 1933. Price, \$4.50.

A third edition is evidence that a book has well filled a certain need. The operative set-up, instruments, position of the patient, preparation of the part and stages of the operation are briefly given. In the appendix the more commonly used instruments are illustrated. The printing and illustrating of this book are superior to those found in most textbooks for nurses.

I. R.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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On the Etiology and Pathogenesis of Whooping Cough.—That the Bordet-Gengou bacillus is the specific causal organism responsible for whooping cough is by no means a settled question, as shown by a recent paper by RICH (*Bull. Johns Hopkins Hosp.*, 1932, 51, 346). The author discusses first Mallory's original work and that of other authors who have proved that the evidence of the specificity of this organism is not at all conclusive, and that it is quite possible that the cough of pertussis may be provoked by organisms other than the specific bacillus whose implication in the cilia of the respiratory tract is responsible for the paroxysmal cough. He shows that it may be possible to reproduce the whooping cough syndrome with cultures of influenza bacilli and that the influenza organism may be entangled in the cilia of the air passage in exactly the manner in which the Bordet-Gengou bacillus localizes. He discusses other features of whooping cough which may be reproduced likewise in other diseases. For example, the mononuclear cell infiltration of bronchial walls which occurs in whooping cough uncomplicated by pneumonia is characteristic of interstitial pneumonia. This pathologic picture occurs almost exclusively in those diseases which are believed to be due to filterable viruses, as for example, measles, influenza or whooping cough. The suggestion is advanced by the author that the lesion of whooping cough may be the result of, or may be produced by an invisible virus rather than by secondary bacterial invaders. He suggests, furthermore, that many of these observations indicate that the invisible virus may play an important rôle in the etiology of whooping cough and he demonstrates instances in which internuclear inclusion bodies in the lungs occurred in cases of whooping cough. These may possibly represent the effect of aspirated herpes virus.

The Prognosis in Cardiac Disorders.—An optimistic and cheerful presentation of the prognosis of the various types of heart disease has been presented by RUDOLF (*Canadian Med. Assn. J.*, 1933, 28, 35). He discusses first disturbances of cardiac rhythm and points out much that is well known, but to be accentuated is the statement that extrasystoles in the absence of other signs of heart disease mean but little. In organic heart disease the statement is made that occasionally subacute bacterial endocarditis is cured, although it is usually fatal within a few months. In syphilitic heart disease gotten early, the outlook is

fairly good if the specific treatment is thorough. In the tertiary cases, death usually occurs within 5 years after heart symptoms have set in, a really rather remarkably hopeful prognosis in this condition. The patient with angina pectoris may die from the disease, but not in the first attack, and the majority of sufferers do not die in an attack, but from subsequent heart failure. Quite commonly if the cause of the anginal attack is discovered, it can be controlled and the patient may go on for some years. With coronary thrombosis most cases are unrecognized, judging from pathologic studies, but in the more severe cases with recognizable symptoms, a larger artery being implicated, the prognosis is extremely grave. He concludes with this word of advice: "A gloomy view may precipitate heart failure when otherwise this might have been long deferred. Many a cardiac hypochondriac owes his condition largely to some indiscreet, and the often quite unwarranted, opinion expressed by an over-anxious medical attendant."

SURGERY

UNDER THE CHARGE OF

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Iodin in Hyperthyroidism.—Iodin in some form or other has been used for the treatment of goiter since ancient times. In recent years NEISSER (*Klin. Wchnschr.*, 1920, 57, 461) stressed the value of potassium iodid in the treatment of exophthalmic goiter and LOEWY and ZONDEK (*Deutsch. med. Wchnschr.*, 1921, 47, 1387) showed quite conclusively its effect on the lowering of the basal metabolic rate. However, the impetus for the use of iodin in the treatment of thyrotoxicosis followed the work of PLUMMER and BOOTHBY (*Col. Papers of the Mayo Clinic and the Mayo Foundation*, 1923, 15, 565; *J. Iowa State Med. Soc.*, 1924, 14, 66). These authors presented data on 400 cases of hyperthyroidism treated by large doses of iodin which corroborated the findings of Loewy and Zondek in regard to the effect of iodin in reducing the respiratory exchange. In most of the earlier work on patients as well as the work on experimental animals in regard to the hyperthyroid state, the iodine was administered in the form of potassium iodid. Plummer and Boothby, however, advocated the use of Lugol's solution instead of potassium iodid "because it is an aqueous solution of iodine and potassium iodid and therefore provides a large amount of iodine loosely combined with potassium." The inference that Lugol's solution is more useful than potassium iodid in the treatment of hyperthyroidism has been rather generally accepted as a fact in this country. In addition the statement quoted above connotes that large doses of iodine are needed. The data presented by THOMPSON, COHEN, THOMPSON, THORP, and BRAILEY (*Arch. Int. Med.*, 1930, 45, 430) refute this idea

since these workers were able to produce as great a fall in the basal metabolic rate with small doses of Lugol's solution as with large doses.

LERMAN and MEANS (*Am. J. Med. Sci.*, 1931, 181, 745) compared the effect of Lugol's solution, potassium iodid and ethyl iodid as to the effect on the basal metabolic rate in exophthalmic goiter and found all equally effective. These results indicate that the type of iodine compound administered makes little difference. Inhalations of ethyl iodid were as effective in reducing the metabolic rate as solutions of inorganic iodine compounds given by mouth.

COHN (*Arch. Int. Med.*, 1932, 49, 950) studied the rate of absorption of iodine from various portions of the gastro-intestinal tract and found that iodine was absorbed readily from all portions of the intestine. He also found that whether iodine was introduced as free iodine, Lugol's solution, or potassium iodid the solutions recovered from the intestine never gave a test for free iodine when allowed to remain in the intestine for as long as 4 minutes. These results explain why Lugol's solution is no more efficacious in alleviating the symptoms of thyroid disease than potassium iodid, since the free iodine in Lugol's solution is converted to iodid before absorption. Since Lugol's solution is more unpleasant to take there appears little rationale in its use in preference to potassium iodid. That free iodine is rapidly converted to iodid in the gastro-intestinal tract is not a new observation since this fact has been stated repeatedly in standard pharmacological textbooks. The studies of Cohn reëmpHASize the rapidity of this conversion. The continued use of iodine solutions over a long period of time in the treatment of hyperthyroidism has been largely responsible for the delay in accepting this efficacious agent for the preparation of patients for thyroidectomy. Shortly after the discovery of iodine by COURTOIS (*Ann. de Chim. et Physiol.*, 1813, 88, 304), COINDET (*Ibid.*, 1820, 15, 49) introduced the use of iodine in the treatment of goiter, but due to the appearance of symptoms which we now understand as the result of overdosage the treatment was discontinued. MARINE (*Medicine*, 1927, 6, 127), FRAZIER and MOSSER (*Ann. Surg.*, 1929, 89, 849) and MOSSER (*Surg., Gynec. and Obstet.*, 1928, 47, 168) explain the untoward effects of continued administration on the basis that in hyperthyroidism, iodine causes an increase in the amount of colloid in the acini, distending the acini, and for a time the metabolic rate decreases as a result of "pressure retention," and later increases as the stage of exhaustion ensues.

THERAPEUTICS

UNDER THE CHARGE OF

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Synthetic Preparations in the Treatment of Malaria.—MÜHLENS (*München. med. Wchnschr.*, 1932, 79, 537) discusses malaria therapy in the light of recent advances in chemotherapy. The therapeutic

use of *plasmochin* (n-diethylamino-isopentyl-8-amino-6-methoxy-chinolin) and *atebrin* (a derivative of alkylamino-acridin) is particularly emphasized. The use of plasmochin in tropical malaria due to gametocytes and in cases with quinin idiosyncrasy is particularly indicated. Its beneficial effect in the tertian form is probably as great as, and in the quartan form probably greater than, that of quinin. In the treatment of larger groups of the population in the tropics the combination of quinin and plasmochin, in the form of tablets, each containing 0.3 gm. of quinin + 0.01 gm. plasmochin (*chinoplasmin*) proved to be very effective. In severe cases administration of 4 to 5 tablets daily up to 21 days usually eradicates the infection, and administration of after-treatment is not necessary. The author claims that chinoplasmin proved to be a most efficacious agent in prophylaxis; 1 tablet is usually taken in the evening. Cyanosis and epigastric pain are observed with relatively larger doses. The author treated 122 cases of malaria with *atebrin* and with a combination of *atebrin* and *plasmochin*. The dosage varied. Usually 0.1 gm. of *atebrin* was given, three times daily, for 3 to 10 days. In some instances, after 4 days without medication, treatment was reinstated. The total amount administered usually did not exceed 4.8 gm. Cases with all three types of malaria responded to *atebrin*. Relapses occurred but seldom. Tropical malaria due to ringform parasites did not improve, as a rule, following the administration of *atebrin*. In such cases quinin was administered intramuscularly for 2 days in addition to the combined administration of 0.1 gm. of *atebrin* and 0.01 gm. of *plasmochin*, three times daily. *Atebrin* was well tolerated by patients with quinin idiosyncrasy and with blackwater fever. *Atebrin* causes yellowish discoloration of the skin. This is not due to liver damage but to the liberation of acridin.

PEDIATRICS

UNDER THE CHARGE OF
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Kernikterus: Jaundice of the Nuclear Masses of the Brain.—ZIMMERMAN and YANNET (*Am. J. Dis. Child.*, 1933, 45, 740) point out that the pathogenesis of kernikterus is that following some injury; the nerve cells are subsequently stained with the bile pigments carried to them by the blood stream. This differs in no way from the well-known fact that any intravital dye will localize in zones of injury and will leave unstained tissues that are undamaged. It was also noted that injured myelin sheaths become jaundiced. This is a further substantiation of the theory mentioned. The question arises as to why the jaundice localizes in the central nuclear masses and so rarely in the cerebral cortex. The final answer to this question is not possible at this time. However, it must be noted that the macroscopic observations on the localization of the jaundice are not absolutely accurate, for, microscopically, isolated nerve cells in both the cerebral and cerebellar cortex are found to contain bile pigment. The gross localization of jaundice

in the basal ganglia suggests close relationship between kernikterus and Wilson's disease. These two conditions have a striking similarity as regards the localization of the cerebral changes, their frequent association with hepatic lesions and the strong familial tendency. On the other hand, Wilson's disease is one of adult life rather than of childhood. There is little in the history of patients suffering with this disease to indicate a lesion existing from infancy. Although jaundice may be present, the basal ganglia are never pigmented. Clinically the symptoms are predominantly those referable to lesions in the basal ganglia, even in those cases which have a picture suggestive of a more widespread cerebral involvement such as pseudosclerosis. In contrast to this, the cases which are diagnosed clinically as kernikterus but in which recovery occurs with sequelæ, show not only symptoms referable to lesions of the basal ganglia but also symptoms of a more diffuse cerebral involvement. The hepatic changes observed in Wilson's disease are in the nature of a fibrosis or cirrhosis, but there is little similarity in this regard in kernikterus. In 2 cases included in this report *B. coli* was found in the blood. Other observers have reported cultural findings. In some cases it has been impossible to show infection, but this may be due to too few blood examinations being made, and the blood should be arterial rather than venous as blood cultures of venous blood are often inconclusively negative as the bacteria may be filtered out through the capillary bed. In 1 of the cases there was evidence of umbilical and hepatic infection although the blood cultures were negative. In the fatal cases of kernikterus no definite clinical picture was seen whereby the condition could be diagnosed during life. An appreciable percentage of the cases that reveal symptoms of icterus gravis show that they may be taken as indicative of involvement of the central nervous system, such as convulsions, spasticity, irregularity of respiration, drowsiness, circulatory instability and vomiting. Of these only a small percentage show kernikterus postmortem. On the other hand, a certain percentage of newborn infants in whom jaundice of the nuclear masses of the brain is demonstrated at autopsy, have revealed during life no definite evidence that might suggest specific involvement of the central nervous system.

Aspects of Phenobarbital Poisoning.—WEIDEMANN (*Monatschr. f. Kinderh.*, 1933, 55, 307) gives the clinical history of a girl aged 3 years, who 9 months before had suffered from measles with a severe bluish exanthem. When the child came under observation, it had had whooping cough for 4 weeks, and had been under treatment with phenobarbital 16 days. For 12 days she had received 4 tablets a day, or a daily supply of 0.06 gm. Then the treatment was discontinued because suddenly the temperature increased to 102.2° F., vomiting began, the pharynx was reddish and the entire body became covered with a light red exanthem. The physician in charge diagnosed the condition as scarlet fever and administered scarlet fever streptococcus serum. In spite of this the exanthem became more severe within the next 2 days, and the general condition became poorer. On the basis of the history and of the clinical manifestations during the first few days, measles as well as scarlet fever were excluded. Phenobarbital intoxication was suspected because the cutaneous manifestations resembled those that have been

observed as the result of another barbituric acid preparation. The incubation period of 8 to 12 days noted in this case resembled that seen in barbituric acid intoxication and the same may be said of the blood picture. Unusual aspects of this disturbance are the mucous membrane manifestations, the extraordinarily large lamellar desquamation and the protracted persistence of the cutaneous manifestations. In this case remainders of the exanthem in the form of pale brownish pigmented spots were visible after 6 months.

The Injection of Maternal Blood in Severe Vomiting of Nurslings.—AUDÉOUD (*Rev. franç. de pédiat.*, 1932, 8, 737) followed this method of treatment in 8 cases. The ages of the patients varied from 5 weeks to 3 months. All presented repeated, abundant, projectile vomiting, had lost considerable weight and were weak and in poor general condition. Injections of 20 cc. of the maternal, or sometimes of the paternal blood, were made every 2 or 3 days by injecting 10 cc. into each buttock. The treatment lasted from 3 to 9 weeks. The initial constipation was gradually replaced by normal bowel movements, the vomiting was gradually cured, and the infants regained the appearance of good health and were able to take normal meals. The increase in weight varied from 650 gm. in 22 days to 1515 gm. in 7½ weeks, the average gain being 1029 gm. Dietetic therapy should be concurrent with the hemotherapy. At first only carbonated water was given in teaspoonful doses but later it was mixed with condensed milk. The amounts were gradually increased as the vomiting subsided. Massage with warm camphor liniment and warm compresses on the gastric region every 2 or 3 hours assisted in calming the violent contractions of the stomach. The mode of action of the injections is not known but the action may be as in anaphylactic diseases.

DERMATOLOGY AND SYPHILIS

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Pyodermia Gangrenosum.—The term pyodermia gangrenosum implies a suppurative destructive process of the skin dependent upon infections of long duration elsewhere in the body. Such a case of unusual severity, secondary to infection of the gall bladder and urinary tract and progressing to fatal issue is reviewed by LANE and STROUD (*Arch. Dermat. and Syph.*, 1933, 27, 460). A number of examples have been reported following ulcerative colitis. The primary lesions of the skin are pustules, papules or small nodules which tend to form undermined deep-seated ulcers. The causative organism appears to be a hemolytic staphylococcus albus and a streptococcus acting in symbiosis. Inocu-

lation of these organisms into rabbits has produced analogous cutaneous ulceration. The treatment should be directed principally toward the eradication of the underlying infection. Pyridium paste exerted a favorable local effect on the ulcers in the case studied by the authors.

GYNECOLOGY AND OBSTETRICS

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Morphology of Genital Epithelia.—The discussion relative to the pathogenesis of endometriosis continues to be a live topic and although Sampson's theory of transtubal transplantation has enjoyed much support it is by no means universally accepted. One of the most insistent opponents to this theory is NOVAK (*Am. J. Obst. and Gynec.*, 1932, 24, 635) who has presented a paper in which he describes the occurrence of certain differentiation anomalies in the epithelium of the various segments of the genital canal. Among them are the occurrence in the tube, of definite endometrial tissue; the occurrence in the ovary of either an endometrial or tubal type of tissue, and even, on the ovarian surface, of stratified squamous areas; the occurrence in the endometrium of either squamous areas or of patches of tubal epithelium; and finally the frequent presence in the normally columnar cell regions of the cervix of stratified squamous "metaplasia" and the occasional presence of a tubal type of epithelium. He believes that such anomalies illustrate the tendency toward intermutability of these genital epithelia under certain conditions, a tendency obviously dependent upon their common origin from the same mother tissue, the celomic epithelium. Cognizance of this fundamental fact must be taken in the interpretation of many pathologic lesions, such as endometriosis where direct transformation of germinal epithelium into either a tubal or endometrial type can be demonstrated histologically, so that it seems to the author unnecessary to invoke the doctrine of implantation in explaining this lesion.

OPHTHALMOLOGY

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Is Retinitis Pigmentosa Due to Vitamin Deficiency.—LEVINE (*Arch. Ophthalm.*, 1933, 9, 453) reviews the literature on retinitis pigmentosa and cites the main facts that are known about the disease. To date it

has remained practically incurable. Heredity seems to be an important factor in its etiology. It is characterized essentially by a primary degeneration of the neuroepithelium and the pigment epithelium of the retina. Its outstanding symptom is night blindness.

The most specific tissue change in vitamin A deficiency is damage to epithelial structures. One of its symptoms is night blindness. Cases of idiopathic night blindness with peculiar white dots in the fundus are reported to have cleared up on vitamin A therapy. It has been demonstrated that the retina contains more vitamin A than any other tissue except the brain and that this is located especially in the region of the rods which are particularly affected in retinitis pigmentosa. However, it has not been demonstrated as yet that the retina, in cases of retinitis pigmentosa, is deficient in vitamin A. The histology of the retina has not been studied in cases of night blindness associated with xerosis or keratomalacia (vitamin A deficiency), or in the idiopathic cases with white dots in the retina. Pillat has found pigmentation of the conjunctiva in patients with vitamin A deficiency. This has not been demonstrated in retinitis pigmentosa. For the last 5 years, the author has given large doses of cod liver oil to all his patients with retinitis pigmentosa. He was at first encouraged by the apparent improvement in vision and enlargement of the visual fields. But the improvement has not been maintained. If retinitis pigmentosa is, after all, due to vitamin deficiency, it may be that the diseased retina cannot utilize vitamin A supplied in the form of liver and cod liver oil.

OTO-RHINO-LARYNGOLOGY

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Asymmetry of the Nares. A Positive Diagnostic Sign or Entity Establishing Anatomic Displacement of Lower End of Cartilaginous Nasal Septum.—In these days when medicine's ancillary and cognate sciences are in the saddle, there is a seemingly irresistible urge to apply basic academic truths to knotty clinical problems in otolaryngology. For instance, there is a geometric proposition that, when a perpendicular is dropped from the apex of an isosceles triangle to its base, the original triangle is divided into two similar or symmetrical triangles; and that if the base of this perpendicular is moved to either side, then these two similar triangles become dissimilar or asymmetrical. Viewing the base of the nose as an isosceles triangle, and the normally situated septum as the perpendicular, METZENBAUM (*Arch. Otolaryngol.*, 1932, 16, 690) applies this geometric proposition, and its converse, to commonly encountered dislocations of the lower end of the cartilaginous septum, and evolves therefrom a clinical principle and several corollaries. Inasmuch as many of these septal mal-alignments result from injuries sustained in infancy or childhood, and inasmuch as their simple reduction can be accomplished soon after the trauma, the importance of their early recognition is too obvious to require further comment here.

RADIOLOGY

UNDER THE CHARGE OF

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Calcification of the Suprarenal Glands in Addison's Disease.—Roentgenologic evidence of calcification of the suprarenal glands in cases of Addison's disease has been presented in numerous isolated case reports, but the frequency with which such evidence can be obtained has not heretofore been determined. Accordingly, CAMP, BALL and GREENE (*Am. J. Roent. and Rad. Ther.*, 1932, 28, 594) have tried to determine: (1) The incidence of calcification in a series of suprarenal glands removed at necropsy in cases of Addison's disease; (2) the incidence of calcification in the suprarenal areas in a consecutive series of patients affected with Addison's disease. The suprarenal glands were obtained in 34 cases which had been listed by the pathologists as Addison's disease or as tuberculosis of the suprarenal glands. A positive clinical diagnosis of Addison's disease had been made in 23 of these cases, and a questionable diagnosis in 3; in the remaining 8 cases there were tuberculous lesions of one type or another. A second group of suprarenal glands adjudged to be normal was also observed for control. Both groups were subjected to roentgenologic examination. Of the 23 cases in which a positive diagnosis of Addison's disease had been made, 6 showed roentgenologic shadows of calcification; of the 3 questionable cases, 2 showed such shadows; of the 8 cases of tuberculous glands, 3 were positive. Thus 32.3 per cent of the entire group showed shadows of calcification. These types of calcification were noted: (1) Gross calcification of the entire gland; (2) multiple discrete areas of calcification; (3) homogeneous increased density of the entire gland, suggesting a diffuse deposition of lime salts. Twenty-three patients having Addison's disease clinically were then examined with the Roentgen rays and shadows indicative of suprarenal calcification were observed in 6.

Juvenile Paresis: Diathermy Hyperpyrexia in a Malaria Resistant Patient.—The case of a boy, aged 12 years, with all the diagnostic criteria of juvenile paresis, is reported by POLMER, from Touro Infirmary (*Arch. Phys. Ther., X-ray, Rad.*, 1933, 14, 23). Vigorous anti-luetic treatment and malarial therapy were employed for 11 months without any subjective improvement or objective signs indicative of arrest or remission. After receiving 12 diathermy hyperpyrexia treatments over a period of 6 weeks the spinal fluid was serologically negative on 2 successive examinations with an interval of 10 days between. The patient was discharged as improved 7 weeks after the series of treatments was commenced.

The Present Status of Electropyræxia.—Various methods of inducing hyperpyrexia are discussed and the techniques of diathermic, radiothermic and blanket electropyræxia are described by NEYMANN, FEINBERG, MARKSON and OSBORNE (*Arch. Phys. Ther., X-ray, Rad.*, 1932, 13, 749). From their experience the authors conclude that, all other factors being equal, the diathermic procedure is the most efficient, the radiothermic next and that the electric blanket is least efficient. They consider the original type of blanket to be a dangerous instrument, because many of its wires are non-insulated and the patient may be burned deeply or electrocuted. A new blanket with insulated wires has been evolved and promises to be safe and efficient. About 60 per cent of the cases of general paresis given electrothermic treatment by the authors and others have been cured or improved, 75 per cent of a small series of patients suffering from multiple sclerosis have derived some benefit, 50 per cent of the authors' cases of asthma obtained long or short remissions and 85 per cent of a selected arthritic group were definitely benefited.

Diathermy in Gynecology.—According to CUMBERBATCH, of St. Bartholomew's Hospital in London (*Arch. Phys. Ther., X-ray, Rad.*, 1932, 13, 782), a cure is confidently expected and almost always obtained from diathermy in gonococcal urethritis in women. Non-gonococcal cervicitis responds equally well to diathermy and the cervix regains its normal condition. In gonococcal arthritis application of diathermy to the cervix brings about relief of pain, reduction of swelling of the joints and increase of range of motion. Further benefit is obtained if the joints are subjected to diathermy, massage and movements. In non-gonococcal metastatic arthritis the same results are obtained in 75 per cent of the patients. In salpingitis, whether gonococcal or not, diathermy should not be administered if pus is present. If it is absent, diathermy causes all signs and symptoms to disappear. In dysmenorrhea of the congestive type in married women diathermy has not failed in any of the cases. On the other hand, it has done no good in cases of the spasmodic type.

The Value of the Roentgen Ray in the Diagnosis of Renal Tuberculosis.—In the opinion of WATERS (*Am. J. Roent. and Rad. Ther.*, 1933, 29, 17) no investigation for renal tuberculosis is complete without satisfactory plain films and pyelograms of the urinary tract. The early Roentgen findings in renal tuberculosis are fringing of the calyces and possibly calcification in areas of cortical necrosis. The author's statistics show a diagnostic accuracy of 70 per cent in the pyelographic series. Areas of cortical calcification appeared on the plain film in 40 per cent of the cases of known tuberculosis. Direct smears yielded only 55 per cent of diagnoses, but guinea pig inoculations gave positive evidence in the other 45 per cent. There are no contraindications to pyelography in renal tuberculosis. Intravenous urography has not yielded the brilliant results expected, chiefly owing to the fact that sufficient concentration of the dye is lacking in so many cases, but with improvement in opaque media and technique, it is possible that great diagnostic accuracy may be achieved.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Mental Reactions at the Climacterium.—JAMEISON and WALL (*Am. J. Psychiat.*, 1932, 9, 895) state that the attitude and behavior of patients at the climacterium is uniformly one of depression, agitation and apprehension. Persistent restlessness, inability to sleep, occasional fretfulness and irritability of varying degree are noted. Suicide is more likely to occur than in any other type of illness and a general indifference to personal appearance and habits is common. These things are all easily recognized. The therapy for a frank case of melancholia is best managed in a hospital, although certain patients may be treated satisfactorily at home. Both physical and psychologic factors should be considered. The physical factors are very important and should receive careful attention. The excessive use of sedatives or opiates is contraindicated. Warm baths, warm packs, elimination of toxic features, regulated exercise, diet and healthy mental contacts are important. On the mental side, one who has the confidence of the patient may do much by a careful review of the history and a frank discussion of physiologic and psychologic forces at work. "Involitional melancholia is probably not a complete clinical entity in itself. The life history of the patient, including family tendencies, physical constitution, personality and psychic forces all have an influence. The period of the menopause with its physiologic changes forms the background for the play of these several factors. Any type of borderline or frank mental disease may appear at this time."

Mental Symptoms in Disseminated Sclerosis.—SALTRE (*Norsk Mag. f. Lægevid.*, 1932, 92, 353) states that of 2000 patients admitted to Vinderen Psychiatric Clinic between September, 1926, and December, 1930, 13 were diagnosed as cases of disseminated sclerosis. Of these, 12 were admitted for their psychic symptoms; 10 patients were females and 2 were males. In 8 the mental disturbances were severe, while the remaining 4 showed a mental state characterized by euphoria, slight dementia, pronounced emotional instability and egocentricity. The author suggests that, until a more specific etiology has been discovered, the term "psychoencephalitis" (invented by Ombredanne) should be applied to atypical cases of disseminated sclerosis with mental symptoms, as well as to similar cases of epidemic encephalitis and parencephalitis. The prognosis is grave; only 1 of Salthre's patients showed an almost complete recovery.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Production of Non-fatal Vascular Sclerosis in Rabbits by Means of Viosterol (Irradiated Ergosterol).—In a series of experiments carried out by SPIES (*Arch. Int. Med.*, 1932, 50, 443) young rabbits were fed by stomach tube a preparation of viosterol, "10,000D," in doses of from 5 to 7 cc. at intervals of from 4 to 5 days. The period of administration including rests for recovery from toxic manifestations totaled from 40 to 70 days. After the final dose of viosterol the animals were killed from 97 to 102 days, and the organs were examined. The lesions found in these experiments situated in the aorta, lungs and kidneys are described and discussed in this paper. The aortas from the animals that had received viosterol showed severe medial sclerosis with varying degrees of hyalinization and calcification. In the kidneys the renal arteries and arterioles, and the renal tubules and glomerular capsules were hyalinized and calcified. Calcium was deposited in the parenchyma of the lungs, but was not seen in the pulmonary vessels. The author considers that these lesions were slightly less extensive than those found in a series of animals which he had previously studied, but that the relative proportion of hyalin degeneration to calcareous deposits was greater than in comparable lesions found in his former experiments. He suggests that the degree of calcification in these tissues was more extensive at some period during active treatment, but that in the interval between the cessation of viosterol administration and the termination of the experiments the animals may have reabsorbed some of the calcareous deposits, thereby leaving a permanent sclerosis of the aorta and vessels of the kidney.

A Functioning Tumor of the Islands of Langerhans.—BARNARD (*J. Pathol. and Bacteriol.*, 1932, 35, 929) presents a case of an adenoma of the pancreas which appeared to have the function of secreting insulin. The patient complained of symptoms and presented signs of hypoglycemia, and was treated by considerable quantities of glucose. She recovered from several severe attacks but died 2 months later from the effects of hypoglycemia. Postmortem examination revealed an adenoma 1.2 cm. in diameter partly embedded in the head of the pancreas. The microscopic picture of this encapsulated mass led the author to believe this tumor to be an overgrowth of cells of the islets of Langerhans. It was considered benign, but was locally invading its own capsule. The author is certain that if the patient had agreed to operation, that removal of this functioning tumor would have resulted in a complete cure. It is pointed out, however, that the tumor would have been difficult to locate at operation, due to its position, but might have been found because of the firmer quality of the adenoma.

Calcified Corpora Amylacea in the Lung (Zur Pathogenese verkalkter Schichtungskugeln, Sog. "Corpora Amylacea," in der Lunge).—SCHILDKNECHT (*Virch. Arch.*, 1932, 285, 466) reports a case of a paretic woman, aged 45 years, in which there was an unusually large number of corpora amylacea in the lungs; one-fifth to one-quarter of all the air sacs were plugged with the concretions, many of which were calcified. Roentgen ray plates taken a year before death showed miliary shadows through both lungs and gave rise to a diagnosis of miliary tuberculosis. (The Roentgen ray picture is in "Lehrbuch der Roentgen-diagnostik" by Schinz, Baensch and Friedl, 3d ed., vol. 2, p. 798). The pathologic examination of the lungs showed a well-marked emphysema, chronic bronchitis and passive congestion. The corpora amylacea were visible and palpable in the gross; they measured up to 0.3 mm. in diameter; a large number of them completely filled the air sacs in which they lay and were adherent to the alveolar walls. They were composed of concentric layers built upon a small central nucleus. Sometimes the central nucleus was made up of anthracotic particles, sometimes of cells, sometimes of structureless débris. The lamina of the concretions varied in thickness and in staining qualities; many of the lamina stained deeply with hematoxylin and appeared to be made up of nuclear débris. These layers contained calcium and iron in appreciable quantities. Tests for amyloid were negative. The author believes emphysema favors the development of corpora amylacea; emphysematous air sacs do not readily empty themselves, tend to collect desquamated cells and secretions which form a coagulum and adhere in layers to a central nucleus. The development of multiple lamina probably takes considerable time. If the concretions lie in touch with the alveolar walls the lining cells become blended with the periphery of the concretion and form new lamina. No explanation is offered for the calcium and iron deposition within the concretions.

The Parallel Incidence of *Filaria Bancrofti* and the β -hemolytic *Streptococcus* in Certain Tropical Countries.—GRACE, GRACE and WARREN (*Am. J. Trop. Med.*, 1932, 12, 493) report on the incidence of *Filaria bancrofti* and β -hemolytic streptococcus in Jamaica, B. W. I. Cultural examination of 100 consecutive abscesses showed that the streptococcus was responsible for only 6 per cent; 90 per cent were caused by the staphylococcus. Only 1 case of lymphangitis was seen, this occurring at intervals in a patient with an elephantoid lower limb. Only 3 cases of elephantiasis were found. They compare this low incidence of elephantiasis and lymphangitis with data obtained in British Guiana and St. Kitts, B. W. I., where a high incidence of the *Filaria bancrofti* and β -hemolytic streptococcus and their manifestations is found. They suggest that elephantiasis in the Caribbean tropics is associated with the presence of many minute foci of the β -hemolytic streptococcus in the corium of the affected part. They point out the rarity of intramuscular and multiple abscesses in Jamaica. In this paper the authors have shown the low incidence of *Filaria bancrofti* and β -hemolytic streptococcus and their manifestations in Jamaica as compared with the high incidence in St. Kitts and British Guiana. All three places are in the tropics where the *Filaria bancrofti* is supposedly endemic, the population largely colored and the requisite mosquito vector abounds.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Blood Cultures of Apparently Healthy Persons.—Numerous reports have been published on blood cultures from persons with various diseases, but the literature is meager concerning blood cultures from healthy persons. In studies on blood cultures in which control cultures have been reported, the incidence of negative cultures among the controls is usually high. Thus, Cecil, Nichols and Stainsby reported negative results in all of 54 control blood cultures made in connection with their work on arthritis. Gray and Gowen in similar studies obtained positive results in only 2 of 71 control blood cultures. One of these came from a patient with thrombosis of the cavernous sinus; the other, from a patient with agranulocytic angina. Cameron, Rae and Murphy recently cultured the blood of 100 healthy dental students and obtained 6 positive cultures, 4 of which yielded *S. aureus* and 2 diphtheroids. It is reasonable to assume that bacteria may enter the blood stream in persons who have acute or chronic infections. One would expect, therefore, with suitable methods, to be able to demonstrate bacteria in the blood stream in apparently healthy persons and theoretically, at least, would expect a higher incidence of positive results in cultures from persons with frank foci of infection. REITH and SQUIER (*J. Infect. Dis.*, 1932, 51, 336) cultured samples of blood from 293 apparently healthy persons. Cultures containing streptococci, diplococci, diphtheroids, *M. catarrhalis*, colon bacilli and obligatory anaërobic rods were considered positive. Positive cultures were obtained from 53 (27 per cent) of 194 persons who had chronic focal infection, while positive cultures were obtained from only 12 per cent of 99 persons who had no demonstrable focus of infection. Pain in joints or muscles, including chronic infectious arthritis diagnosed clinically in 7, was present in 24. Ten (42 per cent) of these gave blood cultures positive for streptococci or diplococci. A seasonal variation in the incidence of positive blood cultures from persons without demonstrable foci of infection suggests that acute respiratory infections may be responsible for some of the positive cultures.

Epidemiology of the 1930 Poliomyelitis Epidemic in Kansas.—BROWN (*U. S. Pub. Health Rep.*, 1932, 47, 1899) points out that acute anterior poliomyelitis is neither necessarily infantile nor paralytic, though called infantile paralysis. The epidemic of 1930 had about 3 times as many cases as in preceding epidemics, but the case death rate was much lower—9.2 per cent against about 30 per cent in earlier

outbreaks. August, September and October accounted for nearly all of the cases in the years studied. Males constituted 60 per cent of cases. Cases were reported in 433 families, but only 19 families had more than 1 case. The author has tabulated the various important symptoms in order of frequency, and also the site of paralysis. It is suggested that many non-fatal cases occur and are not recognized.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MAY 15, 1933

Melanophores in Meninges of Mammals.—W. H. F. ADDISON and DORIS A. FRASER (Department of Anatomy, University of Pennsylvania). In examining the brains of gray Norway rats, both wild and captive, we have found melanotic pigment constantly present in the cranial meninges, and sometimes in the spinal meninges. In adult animals the pigment is readily visible when the brain is exposed. It is not evenly distributed, but is more abundant in definite areas. On the dorsal aspect of the brain the pigment is along the dural vessels between the cerebellum and cerebrum, and in the membranes behind the olfactory bulbs. It often forms a conspicuous area in the pia along the rhinal fissure. Ventrally it is seen throughout the base of the skull, ensheathing bloodvessels and nerves.

The pigment is in typical melanophores. These have a relatively small cell body and long branching processes, 6 to 8 or more in number. Where the melanophores are grouped together they have a syncytium-like appearance, with processes in seeming continuity with one another, but individual cells are also present. They seem to be an insert type of cell, when compared with the skin chromatophores of lower vertebrates.

In the newborn the pigment is not seen grossly. However, when shreds of the meninges are examined microscopically the melanotic cells are seen in certain areas. These cells are scattered diffusely, and do not show the orientation around bloodvessels as they do in the adult. The cells are smaller and are not as deeply colored as they are later on. The position of the nucleus is much more evident than in the adult because of the sparser distribution of the granules overlying it.

Pigment cells have been previously reported in the meninges of a small number of other mammals. Those include man, sheep, cow and baboon (*Cynocephalus papio*). In man they have been reported as especially evident in the meninges of Javanese and Egyptians, but are also found in Negroes, and to a less extent in Caucasians.

In the Norway rats, the pigment is present in all the color varieties which have been derived from it, such as gray piebalds, black piebalds and ruby-eye dilutes. These we have examined from the Wistar colony of Dr. Helen D. King.

Last year before this society, we reported pigmentation in the hypophyses and parathyroids of Norway rats. It would seem that there might be some relation between the pigmentation of the meninges and of the hypophysis, from their contiguity. But the several other species of mammals which have pigmented meninges do not appear to have melanotic cells in their hypophyses, with the possible exception of man. Therefore there seems to be no necessary correlation between the pigmentation of the meninges and of the hypophysis. And even if the pigmentation of the meninges were connected with that of the hypophysis, this would not explain the pigmentation of the parathyroids.

Glycogen Restoration After Exercise in Depancreatized Cats.—F. D. W. LUKENS, C. N. H. LONG and EDITH G. FRY (George S. Cox Medical Research Institute, University of Pennsylvania). MILROY (*Quart. J. Exper. Physiol.*, 1927, 17, 161) and DEBOIS (*Archiv. Intern. de Pharmacodynamie et de Thérapie*, 1931, 91, 65) have stated that the muscles of depancreatized animals do not restore the glycogen lost as a result of exercise. On the other hand, PESERICO (*Proc. XII International Congress of Physiology*) and CLEGHORN and PETERSON (*J. Physiol.*, 1932, 74, 338) claim that such a restoration does occur.

In view of the importance of this question, not only for an understanding of the recovery process after exercise, but also for the mechanism of insulin action, we have reinvestigated this subject, and have attempted a more or less quantitative comparison of the amount and rate of glycogen reappearance in the muscles of both normal and depancreatized cats.

The animals were depancreatized some 8 to 18 days prior to the experiment. They were maintained on insulin, raw pancreas, meat and milk; 48 hours before use all insulin was withdrawn, and during the last 24 hours no food was supplied (water *ad lib.*). The normal animals were also fasted 24 hours before use.

For the experiment all were anesthetized by the intraperitoneal injection of "Nembutal." Both hind limbs were electrically stimulated, the same stimulus being used in all experiments. One limb was immediately frozen *in situ* with solid CO₂ and ether, and the other after various intervals of recovery. In order to obtain the initial glycogen value one fore limb was also removed. By previous experiments it was found that the ratio between the resting glycogen content of the hind and fore limbs was 1.3 to 1. This ratio was used in all experiments to calculate the initial level of glycogen in the hind limbs. It is important to know this value in each experiment in order to determine the amount of reduction of the glycogen due to the exercise, as from this reduction the glycogen reappearing during recovery can be expressed in terms that are comparable from animal to animal. This indirect method of calculation is rendered necessary by the wide variations in initial muscle glycogen content from animal to animal.

The results show quite clearly that the amount and rate of glycogen restoration are identical both in normal and depancreatized animals for periods of recovery of 1 and 2 hours. Approximately some 30 per cent of the glycogen lost has reappeared in this time. However, in some as yet uncompleted experiments where a period of 6 hours

recovery was observed, there appears to be a difference between the normal and depancreatized animals. The normal animals continue to lay down muscle glycogen, while in the depancreatized animals the amounts restored are of the same order as those observed in the 2-hour periods. This would indicate a division of the recovery mechanism into two parts in which the immediate one is independent of the presence of insulin, while the later stages require it.

In conclusion, however, it should be emphasized that considerable amounts of muscle glycogen can be formed in the depancreatized animal following exercise. The source of this glycogen remains conjectural.

Observations on Effort Angina.—L. B. LAPLACE and E. J. WAYNE (Department of Clinical Research, University College Medical School, London). Studies were made of approximately 450 induced attacks of angina pectoris in a group of 12 subjects who stated that the pain appeared only on physical exertion. Two subjects had aortic insufficiency, 4 had a history of sudden coronary occlusion and 6 appeared to be cases of coronary sclerosis. Two cases came to postmortem examination and showed extensive vascular calcification involving the left coronary artery.

Attacks were induced by causing the subjects to walk over a series of two steps until the onset of pain. Blood pressure, pulse rate and respirations were recorded continuously before and after exercise. Control experiments indicate that the pain appears after an amount of exercise which is relatively constant for each subject.

Blood pressure during the pain was often lower than during the pain-free period. It is concluded therefore that aortic dilatation cannot be the cause of the attack. The pulse rate was always elevated during the pain and lower during the pain-free period. In view of the fact that cardiac output is increased by exercise and that, other factors being equal, the O_2 consumption of the heart is known to increase in proportion to the pulse rate, this type of angina pectoris appears to be due to a relative coronary insufficiency in the presence of increased cardiac effort.

Digital pressure over the carotid sinus promptly lowered the blood pressure and slowed the pulse. When these effects were marked, the duration of the pain was significantly shortened. Intravenous injection of atropin sulphate, $\frac{1}{50}$ grain, greatly increased the pulse rate, diminished the amount of exercise necessary to produce pain, and increased the duration of the attack. These results indicate that either (1) the parasympathetic nerves are not vasoconstrictor to the coronary vessels, or (2) the increased work of the heart and not coronary spasm is alone responsible for the production of pain. The latter explanation is the more tenable.

Amyl nitrite shortened the duration of the attack in 10 cases. Nitroglycerin increased the amount of work necessary to produce pain in 7 cases and erythrol titanitrate acted similarly in only 2 cases. The blood pressure during the attack was usually lower than during control observations. The nitrites therefore appear to act only by causing coronary dilatation. The fact that they were not effective in all cases and that their effectiveness was proportional to the strength of the

drug indicated an organic obstruction of the coronary vessels (sclerotic, stenotic, etc.) and that coronary flow cannot be greatly increased by nitrite action in many cases.

No significant effect could be observed as a result of intravenous injection of Euphyllin or oral administration of alcohol. Repeated exercise did not appear to affect the duration of the attack or the amount of work necessary to produce it. — — —

Anserine and Carnosine in Mammalian Skeletal Muscle.—W. A. WOLFF and D. W. WILSON (Department of Physiological Chemistry, University of Pennsylvania). Carnosine and the closely related anserine have been found in the skeletal muscles of a number of vertebrates. We have studied the distribution of these two imidazole derivatives by quantitative and by isolation procedures. We have isolated carnosine and anserine as copper salts from the skeletal muscles of the dog, cat, deer and opossum. The crystal form, composition and melting points were used in identification.

The carnosine and anserine content of certain muscles has been determined by a quantitative method recently reported by the present authors.¹ Horse and ox muscle are high in carnosine but contain little or no anserine; cat muscle has about equal amounts of carnosine and anserine; dog muscle is high in anserine but low in carnosine.

The occurrence of these two related compounds in vertebrate muscle suggests the possibility of an intimate metabolic relationship between the two and some physiological importance for this type of imidazole derivative. — — —

Effects of Alternate Suction and Pressure on Circulation in the Lower Extremities.—EUGENE M. LANDIS and JOHN H. GIBBON, JR. (Robinet Foundation, Hospital of the University of Pennsylvania). According to Poiseuille's law the volume of fluid flowing through a rigid tube is proportional to the fall in pressure along the tube. It seems possible, therefore, that if the peripheral fall in blood pressure could be increased the total amount of blood flowing past an arterial obstruction in unit time would be greater. The fall in pressure through the arterial tree may be increased physically in two ways, (a) by elevating aortic blood pressure or (b) by reducing peripheral blood pressure to a negative value. The first method is impracticable for numerous reasons but it is possible temporarily to reduce capillary and venous pressure by applying suction to the extremities.

An aluminium box was built large enough to accommodate the lower extremity to a point about 6 inches above the knee and strong enough to withstand pressures of -120 to $+120$ mm. Hg. A mercury manometer, communicating with the interior of the box, was equipped with electrodes so arranged that the one-half horse power motor operating an air pump was stopped through an electrical relay, whenever the pressure in the box exceeded or fell below atmospheric pressure by 120 mm. Hg. A valve was inserted between the pump and the box so that for 25 seconds the pump evacuated air from the box while for 5 seconds the pump expelled cooled air into the box.

¹ Journal of Biological Chemistry, 1933, 100, p., cvi.

Alternate suction and pressure increased, by 45 to 78 per cent, the rate at which fluid flowed through a circulation schema. In normal subjects and patients the effects of suction and pressure on circulation were determined qualitatively by measuring skin temperatures under carefully controlled conditions.

In normal subjects it was found that alternate suction and pressure (a) diminished the rate of cooling of an extremity originally warm and (b) in the majority of instances caused an originally cold extremity to become conspicuously warmer. Suction and pressure sometimes failed to affect blood flow in a cold extremity when vasoconstrictor tone was extremely high. As soon as vasoconstrictor tone was diminished slightly blood flow was conspicuously and preferentially increased in the extremity exposed to positive and negative pressures.

The vasodilator response to warming one forearm was studied in normal subjects with and without the use of external pressure changes. It was found that alternate suction and pressure caused the vasodilator response to appear earlier and that the final temperatures reached were definitely higher in the extremity exposed to external pressure changes.

In patients with peripheral vascular disease alternate suction and pressure increased blood flow definitely even though organic obstruction had advanced to such a stage that no rise in skin temperature was obtained when vasoconstrictor tone was completely abolished by immersing both forearms in warm water or by anesthetizing the posterior tibial nerve.

To obtain the maximal effect on blood flow it is necessary to have (1) relatively brief periods of suction; (2) intermitting periods of pressure, and (3) diminished vasoconstrictor tone.

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ORIGINAL ARTICLES.

**A MODERN PLAN FOR A COMMUNITY CAMPAIGN AGAINST
AIR POLLUTION.***

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THE invitation which brought me here is regarded by the Mellon Institute of Industrial Research as fresh evidence that medical associations in this country are giving serious consideration to the problem of air pollution, presumably with a view to exercising leadership in the promotion of preventive measures. This attitude on the part of the College of Physicians is quite in line with the accepted traditions of Philadelphia, the home of internationally famous scientific societies. Mellon Institute feels honored at being asked to collaborate with you in planning for consideration of the abatement of smoke in Philadelphia. Medical societies in other cities will watch what is done here.

Air, Water and Food Purity Equally Important. Pure air is primarily a medical consideration. Logically, its maintenance is a municipal health department responsibility, just as are pure food and pure water. In the presence of city-wide contamination of his food, his water supply or the air he must breathe, the average citizen is helpless to protect himself or the members of his family. He is compelled to take what the city offers him. When aroused to danger, his instinct and his experience tell him to turn to the physician for protection and guidance. In response to a popular demand

* Presented at a stated meeting of the Section on Public Health and Industrial Medicine of the College of Physicians of Philadelphia, March 31, 1933.

of this kind, the medical profession was found in the forefront of the movements which gave municipalities pure food and pure water. A parallel movement for pure air fell short of establishing thoroughgoing control. Generally the prevention of dense smoke was about all that was aimed at. Only now is the public coming freely to understand that other and unregulated products of fuel combustion are much more harmful.

In view of the inadequacy and inconclusive character of existing legislation, and also because prompt action may bring unusually desirable economic benefits, the time seems ripe for the medical profession to reassert its leadership and to make hygienically pure air an accomplished fact. A development of this kind in medical circles would be in line with the rapid growth of preventive medicine, which includes air hygiene. The initiative and guidance of physicians are necessary to the success of the cause of air hygiene.

Since 1911 Mellon Institute has been conscious of the relevancy of medicine in formulating its research, and has consistently sustained medical interests in their work to mitigate air pollution. In that year it turned to the Pittsburgh School of Medicine for study of the hygienic aspects of the smoke problem. Oskar Klotz, then professor of pathology, and his associates undertook the study. Their comprehensive printed report of the damage done to health by products of combustion is recognized as a classic; it has been a standard work of reference for two decades.

At that time we recognized that the engineer was interested because of fuel economy and the effects of the products of combustion on constructional material. We recognized that the economist was interested from the viewpoint of waste, added expense in cleaning, loss of natural daylight and such phases of the problem. But after all was said and done, the most influential fact in the effect of air pollutants, particularly products of combustion, was health. This angle controlled the formulation of the Pittsburgh ordinance, which ordinance has served as a model for similar legislation in many cities. When the Bureau of Smoke Regulation was organized it was placed in the Department of Health—a practice that was widely followed over the country.

With the passage of years, Mellon Institute has seen success achieved in reducing the dense smoke nuisance emanating from the regulated portions of its home city, and it has consistently adhered to its policy of insisting on medical and public health participation. Even now the Institute is sustaining Ralph R. Mellon and his staff at West Penn Hospital in a study which has for its aim the more accurate determination of air-borne diseases.

In the light of the character of these developments, I come before you as one fully cognizant of the high importance of the strictly medical and public health aspects of smoke abatement.

It must be recognized that, because the physician is the store-

house of needed medical information, he therefore is the sound guide in air hygiene. He knows that inhaled solid particles irritate the sensitive membranes of the nose, throat and lungs, and may prepare a predisposition to acute diseases of the respiratory tract; that smoke and dirt in the atmosphere reduce the amount of natural sunlight received; that this reduction is proportionately greater in the shorter wave lengths, particularly in the therapeutic band of ultraviolet radiation, the natural source of vitamin D; that bright, sunny days are stimulating, while gloomy, smoky days are depressing; that smoke and dust aid in the formation and prolongation of fogs, with their coincident effects; and that, in other ways as well, bodily wellbeing is affected. The rôle of the physician is fundamental; he is looked to by the public to point out health hazards and to work for their elimination; and he is equipped to set the standard for atmospheric cleanliness—a standard which the engineer will then arrange to meet. The public commitment of the physicians in a community to a campaign for pure air will have as much force as the combined arguments of all other protagonists.

Smoke Regulation. With exceptions so few as practically to be negligible, cities that have anti-smoke ordinances regulate only dense smoke. Generally speaking, this means that, unless the density is such that it is impossible to see through the column of smoke as it leaves the stack, there is no violation. And even this opaque smoke is permitted for periods ranging from 1 minute in 8 consecutive minutes to 6 or 8 minutes in 1 hour. Thus it is allowable for a stack to smoke continuously, unless the duration of *opaque* smoke exceeds the time limit. And, of course, solids that do not color the smoke stream, and noxious and obnoxious gases, are not included in the prohibition.

Ordinances prescribe that only such equipment may be installed as can be operated within the limits set, with no provision for reducing those limits as an incentive to manufacturers to produce more advanced designs. After this equipment is installed and in operation, enforcement becomes a matter of observation and supervision on the part of the city inspectors. It is obvious that, under such conditions, results will be in direct proportion to the number of inspectors and their efficiency. Cities have not felt justified in employing large enough inspectional forces for close, continuous control. Consequently, while in many communities it has been possible to maintain a fair degree of compliance, in others enforcement has been little more than a gesture.

The volume of stack dirt is proportional to the amount and smoke-making possibilities of the fuel used. The use of automatic stokers and of semi-smokeless boilers, smokeless fuels in boilers not designed for high volatile coal, better firing methods—all have aided in reducing the amount of visible smoke. The good that might be accomplished has been limited by failure to regulate light smoke

and to exercise control over cinder and ash. Then, too, in all except a few instances, private homes and the smaller apartment houses have been exempt from any regulation as to equipment, fuel or smoke. The necessity for control of domestic smoke-making has been very definitely emphasized during the past three winters. With industrial activity at a low ebb, it has been possible clearly to see the part played by the heating plants in maintaining a smoke nuisance.

The wind is depended upon to carry away the finer solids and to distribute them over wide areas. As the carrying power of the wind is proportional to its velocity, it follows that a low velocity will bring higher concentrations in limited areas, often resulting in formation of a smoke pall or aggravation of one already formed.

Smoke abatement as it has been practised has been instrumental in greatly reducing the amount of visible smoke, in effecting material individual savings in fuel cost, in providing a cleaner atmosphere than formerly with a higher percentage of sunshine, and in reducing cleaning and lighting bills. In other ways as well, smoke abatement has been of tremendous benefit. There is no argument against it; but we still have a smoke nuisance, largely because the extent to which smoke and stack dust can be eliminated has not generally been understood.

Early ordinances necessarily were compromises. A minority protest was smothered by a majority belief that smoke and prosperity were inseparably connected; plant owners feared possible unreasonable restrictions through unintelligent or unsympathetic enforcement; limitation of the amount of smoke to be permitted had to be made in the light of current combustion practice and availability of equipment designed without any such definite restriction; home owners did not take kindly to the idea of regulation, although willing and often eager to have the industrial and commercial plants controlled.

Later ordinances throughout the country generally have been patterned after those earlier compromises. As a result, the advance in smoke abatement has been neither as rapid nor as great as it could have been. The market affords better fuel-burning equipment than ever before; a large percentage of these devices could meet requirements much more strict than those now in force. It would seem wise, from the standpoint of efficiency as well as of cleanliness, to take full advantage of what has been done and to press for additional advances.

Further limiting the effectiveness of smoke abatement is the inability of a city to exercise any control beyond its geographic limits. Manufacturing centers usually are surrounded by smaller industrial communities in which there is little or no regulation of smoke. Wind-borne products of combustion from each such community are carried over and into every other in the group, so that

effort on the part of the central city to clean up is made less decisive by the effects of contaminants originating in parts of the area over which it has no jurisdiction. It is obvious that there should be either unified control or uniform regulation throughout the district.

Another reason for the failure of smoke abatement (as it has been carried on) to meet with the full measure of success that might have been expected is that it has not had the continuous active backing of the community. After an ordinance is passed and a city bureau is charged with the enforcement, most of those who were active in stimulating public opinion and securing enactment of the necessary law regard their civic duty as completed. They, therefore, fold their hands and sit back to watch an inadequately manned enforcement machine operate. Gradually, as the road to cleanliness becomes steeper and more rocky, the machine slows up or even slips backward. There is a demand for a new driver, when the fault lies not with him, nor perhaps with the machine; the road-mending force has quit work. To be permanently successful, smoke abatement like any other constructive program must have the solid support of the people. Passivity is much more difficult to combat than resistance.

Stricter Regulation. Considering the fact that equipment is available to satisfy much more stringent requirements than are now being applied with more or less success, it is comparatively easy to indicate the limits to which existing ordinances could be raised or which could be set for new ones.

1. By proper selection from among the large number of makes of boilers, furnaces, automatic feeds and control, and with intelligent care, *dense* smoke could be eliminated in normal operation. The allowance for *light* smoke would vary; in communities where only smokeless fuel is used, restriction could be greater than in sections where high volatile coal is used and where the degree of smokelessness depends upon the equipment and its operation and not on the fuel.

2. Alterations and repairs could be made to conform to such rules and regulations as would insure the same degree of smokelessness.

3. A reasonable time could be allowed for compliance by those whose plants were installed before restrictions were imposed. Serviceable units need not be scrapped, but could be regulated within reason.

4. The use of dust separators would make it possible to eliminate most of the ash nuisance from solid fuels.

5. Ordinances should allow no exemptions—there should be no preferred class. Laws should be framed in such a way that, without the necessity of formal revision by councils, advantage may be taken from time to time of the rapid advances that will be made toward smokeless and dustless use of fuels.

Campaign for Pure Air. The familiar type of smoke abatement campaign has features which must be included in any movement toward pure air. It provides for the essential stimulation of public opinion; it affords an opportunity for a considerable amount of valuable general education; it prepares the way for needed legisla-

tion. All of these are necessary, and every community has some public-spirited persons, accustomed to lead in civic matters, who will be found willing to organize and direct that part of the work.

More than this is necessary, however. As a physician first examines his patient, makes his diagnosis, then gives him the necessary treatment; so, in a campaign looking toward pure air, it is requisite to determine the nature and extent of the pollution and to ascertain the sources and causes, when the remedy in the form of regulations can be applied.

Logically, the first step is the organization of an air hygiene district, to include all parts of the smoke area, and the selection of a group to constitute an Air Hygiene Commission. The membership of this group should include representation from the medical, chemical, engineering and architectural professions; the financial, manufacturing, commercial and real estate groups, and the local government.

Survey of Atmospheric Pollution. To secure information as to the extent of pollution by products of combustion, actual measurements must be made. Some of these are direct, as the amount and chemical composition of sootfall, and the number and size distribution of air-borne solids; others are indirect, as the effect of air pollution in screening out sunshine, particularly in the ultraviolet region.

Sootfall. The collection of solid matter that falls by gravity or is brought down by rain. The smoke area is divided into districts, according to the number of stations deemed necessary to give the desired results. Naturally the greater the number of such stations, the more accurate the information as to conditions in small sections of the area. Proper containers are placed at the stations, to collect solids that fall by gravity or are brought down by rain. These collectors, when changed periodically, are conveyed to the laboratory, where the deposit can be weighed and analyzed for tar, combustible other than tar, ash, etc.

Information then will be available from which to make a dirt chart of the city, so far as sootfall is concerned, to note variations from time to time and, in connection with other data secured in ways that will be mentioned, to make comparisons as to current conditions, including health.

Air-borne Solids. There is an intermediate size range of particles that, at a fairly high wind velocity, will be carried in suspension, but at a lower wind velocity will fall. Such particles may be picked up, carried awhile and dropped, and this process repeated many times. These, with particles that are gravitating normally to the earth, and other particles so small as to remain in suspension indefinitely, are the air-borne solids which must be measured.

There are several methods of accomplishing the result. One such will give continuous record of the effect of such particles in

discoloring filter paper; another will collect an average sample over a period of time and permit microscopic study of the solids; still others are designed for instantaneous sampling, followed by determination (microscopically) of the number and size distribution of the particles. In a survey of any magnitude, a combination of these likely would be used. The last-named type has the advantage of ready portability, so that one person may take a number of widely distributed samples in a day.

Sulphur Dioxid. The concentration of sulphur dioxid, if desired, may be determined by a standard method.

Natural Sunshine. This is a free gift, to utilize which the human organism was developed through the ages. In building up his cities, man has placed a smoke and dirt screen between himself and the sun, so that he no longer receives all of the benefits to which he is entitled from the source of energy. To obtain knowledge of the extent to which this screen exists in smoky sections, compared with a clean suburb, for example, or the country, measurement of natural solar radiation is essential. The survey should include determination of the infrared, the visible and especially the ultraviolet radiation.

Due to the recent development in photoelectric cells, it is possible to secure continuous records of a part of the infrared, of the visible and of the ultraviolet radiation. For the central station and any other control stations that are set up, the records should be continuous. For readings at other stations, or elsewhere, a portable set, with indicators, can readily be devised.

Other Meteorologic Data. Temperature, relative humidity, sky conditions, rainfall, wind velocity and direction are recorded by the United States Weather Bureau. This information is available for correlation with the data from the sootfall, air-borne solids and sunshine studies.

Upon this knowledge of the amount and character of deposited and air-borne impurities to which the urban dweller is subjected, and of the amount of solar radiation, particularly in the ultraviolet, of which he is unnecessarily deprived, the physician will be able to base his advice.

This survey of atmospheric pollution is the part of the air hygiene program in which the physician will find most interest; the fact-finding is fundamental, and is necessary to show the magnitude of the nuisance and the extent to which it should be abated.

The scope, details and complexities of a study of atmospheric pollution, as outlined above and in paragraphs which follow, may not be generally understood; its necessity may not be appreciated. But, in the light of known damages and demonstrable benefits, science says the city of the future will collect regularly such information as an integral part of its public health work. Science foresees a city population which will view preventable air pollution with

the same intolerance it now displays toward water and food supply contamination.

Sources and Causes of Pollution. A survey, directed by mechanical engineers, should be made to determine the present condition of fuel-burning equipment, with special reference to its classification as: (1) Obsolete or worn out; (2) needing extensive alteration or repair; (3) requiring only minor repairs; (4) indicating change in fuel or firing method only as necessary.

There should be a comparative study, directed by engineering talent, of fuel-burning equipment and fuels offered on the local market, with a view to determining possibilities in efficiency, economy and cleanliness.

Such studies are particularly timely, because of the almost universal undermaintenance during the past 3 years, which has resulted in a country-wide need for replacement of a great deal of fuel-burning equipment and extensive alterations and repairs to much more, to prepare industrial and commercial plants for efficient operation when the present emergency ends. Then there is the vast number of heating plants that need to be replaced or repaired, or in which a different type of fuel should be used. There is an unprecedented amount of work that will have to be done to bring the plants to a condition equivalent to that before the crisis, to say nothing of making any advance toward clean air.

As information concerning conditions and needs is collected and classified, there is the opportunity to put local labor to work on the large volume of minor repairs. Major repairs and alterations can be equitably distributed among responsible local contractors. On new work, because of the information which will have been gathered by the commission, attractive prices and terms undoubtedly can be arranged.

Naturally, this is not the only plan that can be followed. It is given here in brief outline to stress the importance of a comprehensive program, to show how it may be possible to set up such standards of clean air as are feasible, and at the same time to do its part in aiding the unemployment situation and to assist owners to secure advantage of exceptional prices and terms for necessary new equipment.

Legislation. At the proper time, and in the light of the information gained in the surveys, the commission will be in position to recommend standards to be met (a) by new equipment, (b) in alterations and repairs and (c) by other boilers and furnaces that are currently serviceable. These standards may be embodied in an ordinance for the air hygiene district.

Economic Applications. Large-scale application of this or some similar type of campaign plan for pure air might bring economic results which would tie in with work programs that may be developed by municipal, state or federal governments.

A strong demand for fuel-burning equipment easily could step up the work schedule in a number of boiler and stoker plants where employees are idle or on part time. Even mass production might be attained and make possible the lowering of costs, especially to the domestic purchaser.

More distantly a pure air campaign would spur scientific research, which has lagged in some directions, to the task of developing yet more efficient and additional types of appliances and thus broaden the market. The perfecting and marketing of small-size dust separators would become an important industry. A wide market awaits a small stoker, priced within the reach of the "little" home owner.

Cleaner city air will be of vital assistance in the development of the air conditioning industry in smoky cities, by permitting installation of smaller and less costly systems. Currently filtration devices are made large, at consequent greater cost, to take care of "smog" conditions. Also, in smoky centers of population the filters have to be renewed or cleaned more often than should be necessary.

Real estate owners will realize what the smoke nuisance has cost them in the past, and will see the advantage in including air pollution abatement in any rehabilitation program.

Summary. We have tried to show that city dwellers have a right, as a matter of public health, to expect the standard of air purity will be brought up to a parity with that already fixed for water and food; that the rôle of leadership in this movement belongs to the medical profession; that current conditions are unusually favorable for campaign success; that a workable plan of campaign would help immediately to reduce unemployment, spur scientific research, aid infant industries and assist in the restoration of real estate values.

In conclusion, be assured that in connection with whatever action you may take you are free to call upon Mellon Institute of Industrial Research for any assistance it may be able to give, in the light of its 20 years of scientific investigation of the problems of air pollution.

THE RADIOLOGIC RECOGNITION OF HEART DISEASE IN PNEUMOCONIOSIS.

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THE object of this communication is the consideration of a roentgenologic sign of cardiac disease. First, it is to be emphasized that the importance of this is not generally understood. Then, as a contribution to cardiac radiology, it will be demonstrated that

this sign may be used to diagnose specifically a pathologic heart condition caused by pneumoconiosis.

The silhouette of a normal heart, in the postero-anterior roentgenogram, presents a depression on the left border between the aortic "knob" above and the prominence of the left ventricle below. When this depressed area is replaced by a marked convexity it indicates prominence of the pulmonic artery and conus arteriosus. This fundamental observation was made by Assmann.¹ Slight prominence of the shadow may be seen in otherwise normal hearts of the hypoplastic type. When it becomes large enough to reach a line drawn from the aortic to the left ventricular prominence, it represents enlargement and serves as a sign of right ventricular hypertrophy. This is in accord with East and Bain,² who state that with enlargement of the right ventricle "the shadow of the pulmonary artery becomes more prominent, so that the general concavity of the left border becomes filled." Nichols,³ in conjunction with pathologists at the Philadelphia General Hospital, has followed cases with similar cardiac silhouettes to the postmortem table, and reports the shadow to represent enlargement and hypertrophy of the pulmonic artery and the adjacent conus.

Surveys of the American literature reveal no mention of this important fact previous to 1932 when Nemet⁴ stated that "such a configuration of the left cardiac contour indicates marked enlargement of the part of the right ventricle lying between the apex and the pulmonary orifice (so-called outflow tract)."

Right ventricular hypertrophy may thus be recognized in cases of mitral stenosis or congenital heart disease. According to East and Bain² it may be found also in emphysema. Kerley⁵ notes (in quoting both Assmann and Schinz) that enlargement of the pulmonary artery may be due to certain acquired diseases which cause stasis in the pulmonary circulation, notably mitral stenosis, Ayerza's disease, and fibroid phthisis. Nemet⁴ remarks that the "recognition of right ventricular enlargement is of great significance, and is the only indication of structural change of the heart in the important group of cardiac insufficiency developing in cases of long-standing pulmonary fibrosis."

Practitioners in the anthracite coal regions recognize that cardiac failure is a frequent cause of death in pneumoconiosis. A definite cardiac lesion is generally not diagnosed, however, since there is no enlargement of the transverse diameter of the heart. It is my purpose to point out that pneumoconiosis, a disease of long-standing pulmonary fibrosis, causes obliteration of much of the vascular bed in the lungs. It is reasonable to suppose that the first chamber of the heart to show reactionary change is the right ventricle. The proposition is made, therefore, that the convex shadow of the left border described above (when observed in miners with no other indication of heart disease) be regarded as evidence of right ventric-

ular hypertrophy caused by pneumoconiosis. The following cases exemplify the proposition.

Case Abstracts. CASE 1.—J. K., a white male, aged 49 years, was admitted to the White Haven Sanatorium with a provisional diagnosis of tuberculosis complicating pneumoconiosis. He complained not only of cough and expectoration but also of swelling of the ankles. He had been a miner for 27 years and had used the jack-hammer for 5 years. Observations made by Dr. Ross K. Childerhose of the sanatorium staff at that time (1931) included: "Temperature was always normal. He was 12 per cent underweight, and had slight cardiac decompensation. There was moderate cough with 3 fluidounces of expectoration daily. Eighteen sputum examinations were negative for tubercle bacilli as well as two 24-hour collections for concentration and culture methods." In August, 1932, he was brought to the Hazleton State Hospital for study. There was no history of rheumatism or syphilis. Physical examination was negative except for moderate emaciation and a fairly loud to and fro murmur over the pulmonic area. Blood Kahn test was negative. A roentgenogram made at this time was no different from that made at White Haven which disclosed pneumoconiosis, shadows suspicious of tuberculosis, and enlargement of the pulmonary artery and conus shadow. Electrocardiographic examination showed right axis deviation (Fig. 1).

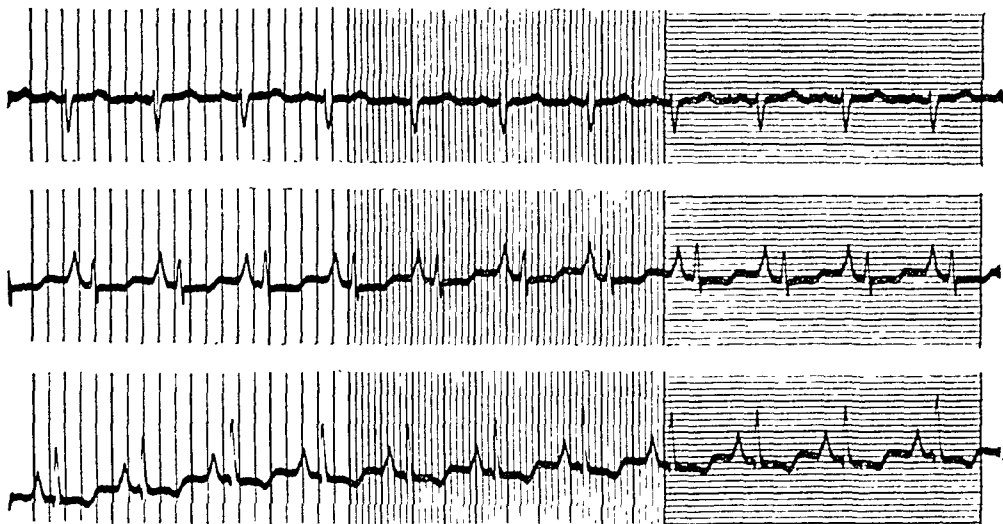


FIG. 1.

Comment. The roentgenogram (Fig. 2) shows no enlargement of the transverse diameter of the heart. The sign of right ventricular hypertrophy can be demonstrated quite definitely, however.

CASE 2.—A. G., a frail white man, aged 51 years, a miner for more than 30 years, admitted to the medical service on September 21, 1931, presented weakness of the arms and legs, in addition to cough, expectoration and substernal pain. Physical examination showed a rapid but regular heart action. Cardiac sounds were "distant and diminished in intensity." Fine râles were heard in each base. Moderately advanced arteriosclerosis was present. No other observations were remarkable except the neurologic examination which disclosed progressive spinal muscular atrophy. Laboratory findings, including blood and spinal fluid Kahn tests, were normal.

Roentgenologic examination showed third stage pneumoconiosis and a very prominent pulmonary artery and conus shadow. This man left the hospital against advice 4 days later, and died at home in April, 1932. No electrocardiogram was obtained.

Comment. The roentgenogram (Fig. 3) confirmed the clinical impression of heart disease.

CASE 3.—M. F., a white male, aged 52 years, came to this hospital in September, 1932, with symptoms of cough, dyspnea, and swelling of the ankles, worse in the last 2 weeks. He had worked in the mines for 10 years, and had handled the jack-hammer for more than 1 year. There had been no rheumatic symptoms, no tonsillitis, and no venereal infections in his past history; his wife had had 6 children (5 living and well) and no miscarriages. There were no other noteworthy facts in his history. Physical examination revealed dyspnea, slight enlargement of the area of cardiac dullness to the right, exaggeration of the pulmonic second sound, râles in each base, and edema of the ankles. Blood Kahn test was negative. Roentgenologic chest examination reported third stage pneumoconiosis and hypertrophy of the right ventricle of the heart. Right axis deviation was found on the electrocardiogram (similar to Fig. 1 and Fig. 6). This man, slightly relieved by hospitalization, returned to his home and is still living.

Comment. Right-sided hypertrophy here (Fig. 4) has not only "filled out" the left border of the cardiac silhouette but has caused enlargement of the transverse diameter to the right.

CASE 4.—J. G., aged 45 years, was a miner for 26 years, using the jack-hammer for the last 7 years. Because of cough, weakness and blood streaked sputum he had been admitted to the White Haven Sanatorium for a month in August, 1932. There was no fever during that time. Moist crackling râles were found in the lower half of each lung, as well as extensive consolidation in the upper halves. Eleven sputum examinations were negative for tubercle bacilli. In October, 1932, he came to the Hazleton State Hospital because of distressing cough, expectoration and anorexia. Nothing in his past life suggested syphilis or rheumatic fever. Prominent findings included emaciation, copious thin expectoration, marked decrease of respiratory excursions, loud moist râles throughout the chest, and an accentuated pulmonic second sound. Urinalyses and blood counts were not abnormal, and the Kahn test proved negative. Roentgenologic studies showed third stage pneumoconiosis and a cardiac shadow suggestive of pulmonary artery enlargement. Electrocardiography produced a tracing of right axis deviation (similar to Fig. 6). After 2 weeks' hospitalization during which he received insulin and the high caloric régime advocated for emaciation, this patient gained 6 pounds and improved enough to be discharged to the dispensary.

Comment. Fluoroscopy demonstrated the pulmonary artery prominence more conclusively than the roentgenogram (Fig. 5). The reactionary enlargement of this structure here might be caused by the drag of adhesions as well as decrease in the pulmonary vascular bed. This would be in agreement with Dietlen,⁶ who cites as a case in point chronic pulmonary tuberculosis with fibrotic lung tissue dragging on the pulmonary artery. Kerley,⁵ and Pancoast and Pendergrass⁷ also admit of this possibility.

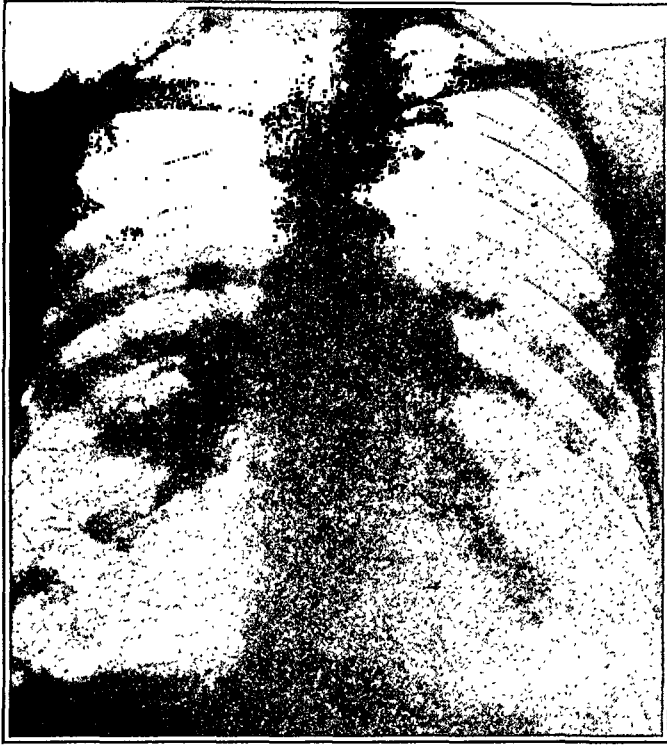


FIG. 2.—Case 1. Roentgenogram shows difficulty of excluding tuberculosis. Left cardiac border presents prominent shadow of the pulmonary artery and conus.



FIG. 3.—Case 2. Roentgenogram taken September 22, 1931. In addition to the pneumoconiosis the shadow on the left border of the heart is clearly seen.

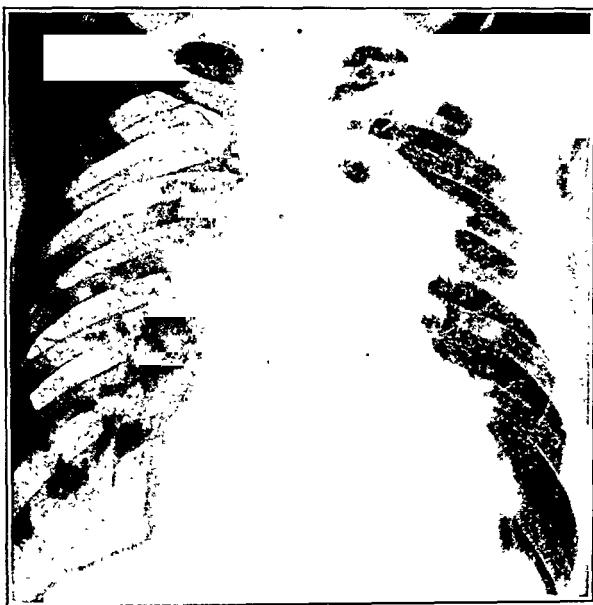


FIG. 4.—Case 3. The left cardiac border is filled out. Right ventricular hypertrophy.



FIG. 5.—Case 4. No enlargement of the transverse diameter of the heart. Pulmonary artery and conus prominence indicate reaction of the right heart to the marked pneumoconiosis.

CASE 5.—H. C., a white male, aged 43 years, was referred to this hospital in October, 1932, for gastro-intestinal studies. His presenting symptoms of diarrhea and lower abdominal discomfort were of only 2 weeks' duration. He had suffered, however, with cough, dyspnea and some dysphagia for 6 months. These were becoming worse instead of better. For 17 years he had worked in the mines, and for 6 months had used rock drills and jack-hammers. He had never had rheumatism, tonsillitis or syphilis. Three children are living and well and his wife had had no miscarriages. Physical examination disclosed nothing remarkable other than limited respiratory excursions, evidence of fibrosis in the upper lobes, and loud, coarse râles throughout the bases. Laboratory studies including the Kahn test were negative. Roentgenologic study of the chest showed third stage pneumoconiosis, most marked in the upper halves of each chest, and a cardiac silhouette indicative of pulmonary artery and conus prominence. An electrocardiogram was made which showed no abnormalities except right axis deviation. After these examinations were completed the patient returned home. No organic disease of the stomach or intestines could be demonstrated.

Comment. The roentgenogram is similar to Fig. 5. The electrocardiogram (Fig. 6) shows the same feature observed in Cases 2, 3 and 4: inversion of the main deflection of the Q-R-S complex in Lead 1.

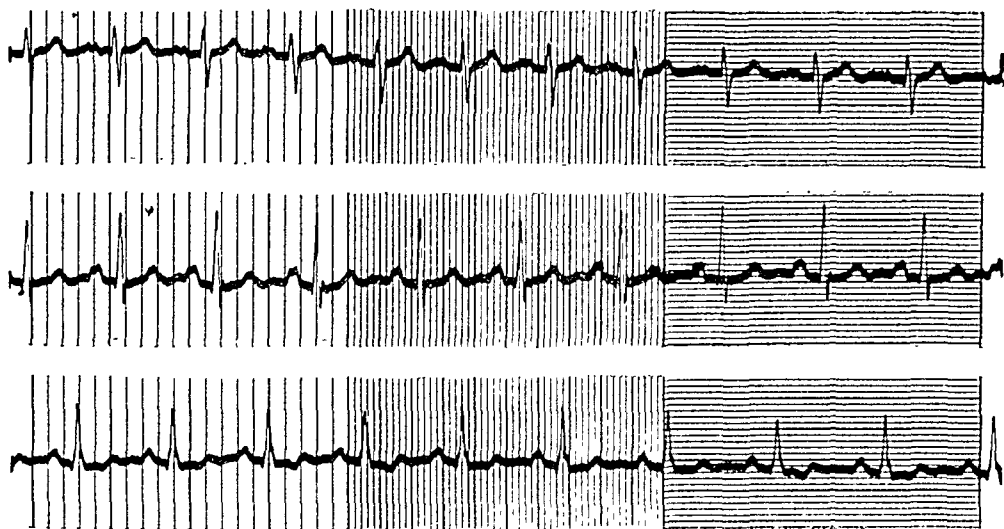


FIG. 6.

Summary and Conclusions. 1. The roentgenologic sign of hypertrophy of the pulmonary artery and the right ventricle is described, and its importance emphasized.

2. Five cases, with their roentgenograms, are presented to demonstrate how this sign may be utilized to diagnose right ventricular hypertrophy due to pneumoconiosis. Electrocardiograms were made in 4 of these cases, each of which presented right axis deviation.

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THE HEALING OF TUBERCULOUS CAVITIES: A CLINICAL STUDY.*

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THE prognostic significance of an open cavity in a tuberculous patient, particularly at the time of discharge from a sanatorium, is generally recognized. In 1916 King¹ showed that patients discharged from Loomis Sanatorium with sputum which had changed from bacillary to non-bacillary had a mortality at the end of 5 years of 225 per 1000, as compared to 710 per 1000 of those in whose sputum tubercle bacilli were demonstrable at time of discharge. Obviously the curability of tuberculous cavities is of first importance, and yet the literature on the subject is replete with conflicting views. According to Gräff,² the presence of cavity portends the death sentence for the patient. He modifies this remark by stating that this sentence frequently is not carried out for several years. Barnes and Barnes,³ in a study of 1454 tuberculosis cases with cavity found a mortality of 80 per cent within 1 year. In contrast with this figure Fales and Beaudet,⁴ in 120 cases with cavity, reported 48 (40 per cent) healed spontaneously. These cases represented 147 cavities, 62 (42 per cent) of which healed. Fischel⁵ found that in those cases receiving institutional care but no other form of treatment, results were so disappointing that he concluded that the existence of pulmonary cavity in poor patients calls for a more

* Paper read before the American Sanatorium Association (Eastern Section) at Waltham, Mass., October 14, 1932.

active therapy, the aim of which should be the obliteration of cavities before the patient is discharged.

In order to reconcile these conflicting and extreme views, and to determine, if possible, significant prognostic factors as to the curability of cavity, a detailed study was made of 296 cases with tuberculous pulmonary cavities at Loomis Sanatorium.

Plan and Scope of Study. Only those cases were included in this study that had cavity demonstrable roentgenographically and tubercle bacilli in the sputum. The minimum period of our observation was 3 months, the shortest period considered to be sufficient to establish at least a trend in the course of the disease. There were but few, however, in this minimum observation group, the average period of observation of the whole group being about 13 months. Cases were taken consecutively from the files of Loomis Sanatorium over a period of 3 years (1928 to 1931); of the 800 cases examined only 296 fulfilled the criteria for inclusion. The following factors were recorded in each case: age, sex, period of observation, side of lesion, size and location of cavity as observed on stereoscopic P. A. Roentgen rays, type of cavity wall and nature of surrounding infiltration; estimate from the history of the duration of the disease and cavity; the amount and bacillary content of the sputum; constitutional reaction (temperature, pulse rate, toxemia); complications; status of body weight as compared with standard; diagnosability of cavity from physical signs and changes in physical signs; duration of bed rest and exercise. Notation was made of the significant changes in the serial Roentgen rays and all the above factors correlated for that particular time. The induction of collapse therapy was indicated and progress thereafter reported.

Since it is of primary importance to determine what actually can be expected in the way of spontaneous healing of cavities, the 296 cases were first classified according to the criteria listed below. If they received no collapse therapy this classification was final. If they received collapse therapy they were classified first on the basis of the changes that had occurred spontaneously and then again to show the results of collapse therapy. In order to avoid confusion in cases receiving collapse therapy soon after admission, an arbitrary time limit of 2 months was set, and all cases receiving collapse therapy within this short period were classified in a separate group, the *Early Collapse Therapy* group, according to the result of this therapy. Thus we have an initial classification arrived at on the basis of spontaneous healing, plus the "early collapse therapy" group, and final classification after adding in the results of later collapse therapy.

The criteria for the initial, and for our purpose most important, classification were as follows: 1, *Spontaneous closure*—sputum negative on concentration for at least 3 months; the shadows representing cavity to be no longer present on the Roentgen ray. 2, *Much*

improved—marked shrinkage in size of cavity, which should not exceed 1 by 1 cm.; sputum negative or positive. 3, *Slightly improved*—total cavity reduced in size, but in excess of 1 by 1 cm. 4, *Unimproved*—Roentgen ray and pathologic anatomy substantially unchanged or worse, irrespective of clinical improvement. Clinical improvement as evidenced by gain in weight, reduction or disappearance of fever was recorded, but did not influence the final classification. Thus, according to the American Sanatorium Association, a patient might be classified as *quiescent*, but in our study would be *unimproved* because of the essentially unchanged pathologic anatomy.

TABLE 1.—RESULTS OF TREATMENT BY BED REST ALONE AND AFTER COLLAPSE PROCEDURES.

	Results of treatment by bed rest alone (spontaneous healing).	Received collapse therapy after observation.	Results of collapse therapy.		Final results, combining spontaneous healing with collapse therapy.
			Cavity closure secured.	Other changes in status.	
Cavity closure secured . . .	65* = 22%	115 = 38.8%
Much improved	38 = 13%	3 { 1 P 2 Ph	2 { 1 P 1 Ph	1 remained much improved	72 = 24.3%
Slightly improved	47 = 15%	23 { 8 P 12 Ph 1 P+Ph 2 Th	8 { 1 P 5 Ph 2 Th	6 became much improved 9 remained slightly improved	53 = 17.9%
Unimproved	84 = 28%	57 { 39 P 17 Ph 1 Ph+Th	13 { 10 P 3 Ph	18 became much improved 9 became slightly improved 17 remained unimproved	56 = 18.9%
Given early collapse therapy (No preliminary observation)	62 = 21% 54 P 8 Ph		27 { 20 P 3 Ph 1 Ph+P 3 P+Th	12 became much improved 11 became slightly improved 12 were unimproved	

* All figures refer to cases, not individual cavities.

P = received therapeutic pneumothorax; Ph = received phrenicectomy; Th = received thoracoplasty.

Application of these criteria for classification gives us the figures of Table 1. The 296 cases, classified according to the Sanatorium Association classification, were divided into 36 per cent "moderately advanced" and 64 per cent "far advanced." The number and percentage of the 5 major groups are shown first. There were 65 cases (22 per cent) in the spontaneous closure group. To make the study complete the subsequent course of the other groups and the influence of collapse therapy on their final status, is indicated. The question may be raised: Why did not more (only 3 of 38) of the "much improved" group later receive collapse therapy, in contrast with the "slightly improved" and "unimproved" groups, of whom 50 and 60 per cent respectively, received collapse therapy?

The reason is that these patients were too well for such therapy and from their past favorable progress it was reasonable to anticipate spontaneous closure. Of the 23 first classified as "slightly improved" and then receiving collapse therapy, 33 per cent obtained closure. Of the 57 first classified as unimproved prior to collapse therapy, 22 per cent obtained closure. Of all who received collapse therapy in these groups 24 per cent obtained closure. Of the 63 in the "early collapse" group, 37 per cent obtained closure and an additional 6 per cent by supplementary surgical procedures. Summing up the results obtained in the whole group shows 65 (22 per cent) obtaining closure spontaneously and 50 (17 per cent) obtaining closure as the result of different forms of collapse therapy. Thus a total of 115 (39 per cent) of the 296 cases eventually were classified as arrested disease.

The markedly higher percentage of closure recorded for the early pneumothorax group (37 against 24) immediately attracts attention and demands explanation. The answer, after analyzing the cases in the two groups, appears to be that it is rather the type of case than the early collapse that gives a higher percentage of closure in the early collapse group. Of 54 early pneumothorax cases, only 4 (7 per cent) had excavation in the contralateral lung, while in the later group of 50 cases, 26 (52 per cent) had cavity in the so-called "good lung." In many instances in the latter group, pneumothorax was withheld until healing changes were demonstrated in the contralateral lung. In others pneumothorax was given in spite of obviously unhealed or unhealing cavities in the hope of obtaining benefit from control of the main focus of disease. In several cases bilateral pneumothorax was given.

Analyses of Factors Influencing Healing. *Side of Cavity.* The frequency of right to left to bilateral cases was 42 to 27 to 31. In this series the incidence of cases with cavity only on the right was definitely preponderant. Furthermore, in considering the 65 cases which satisfied the criteria for spontaneous closure, the incidence of healing was greater on the right—more than twice that of left-sided and three times that of bilateral cases. While this series is too small to draw conclusions from these figures, it is felt that at least a trend is indicated in favor of the right side.

Sex. In the group studied there were 170 men and 126 women. Practically the same percentage of both sexes appeared in the spontaneous closure group and in the unimproved group. It is felt, therefore, that in any large group the factor of sex plays very little part.

Age. In considering age and sex together, however, particularly in different age groups, significant deviations from the average are noted in the percentage of spontaneous closure and of unimproved. The per cent of spontaneous closure for the whole group was 22. Under 25 years, the percentage chance of spontaneous closure was

17. Under 20 the percentage chance of closure for girls was even more significantly less, namely, 11 per cent. Furthermore, the percentage of unimproved was highest in girls under 20 (64 per cent *versus* 28 per cent average). Significant deviation from average in unimproved was also noted in the age group over 45, where a percentage of 40 (*versus* 28 average) was recorded. In other words, resistance to tuberculosis appears to be lower in middle age and adolescence, particularly in young girls.

Average Period of Observation. The spontaneous closure group had the shortest average stay (10.6 months). This figure showed increase in the other groups up to 15.9 months as a maximum in the unimproved group. In other words, in terms of the average, the closure group did well fairly quickly, and length of stay in the other groups was longer in proportion to severity of disease and poor resisting powers. The figure for the early collapse group (11.6 months) is comparatively low, and may be explained by the fact that a number of this group returned home after getting a stable pneumothorax, and obtained refills there. As closely as could be estimated, the average length of time for spontaneous closure by our criteria was 5.6 months. This figure is of interest in comparison with the average time for closure in successful pneumothorax cases (5 to 6 months) as reported by Herben and Franklin* in a study of therapeutic pneumothorax at Loomis Sanatorium.

The Age of Cavity. This cannot be estimated accurately from the history. In this study cavity was considered present from the date of the first hemoptysis or first bacillary sputum or appearance of suggestive cough and expectoration. Using these criteria, the average age of cavity for the closure and unimproved groups was, respectively, 5.4 months and 11.1 months, figures roughly proportional to the number of heavy-walled cavities in these groups.

Body Weight. Increase in body weight is usually a favorable sign, but not always so. As a general rule, patients and the laity place more emphasis on it than on any other single symptom. The status on admission of the 296 cases was: 39 (13.1 per cent) above standard, 249 (84.1 per cent) below and 8 (2.7 per cent) standard weight. At the end of the period of observation, 227 (76.6 per cent) had gained weight, 62 (20.9 per cent) lost and 7 (2.3 per cent) remained stationary. Analysis of changes in body weight in groups according to final status showed, in the closure group of 65 cases, 56 (86.1 per cent) gained weight, 6 (9.2 per cent) lost and 3 (4.6 per cent) remained unchanged. In the unimproved group of 83, 51 (61.4 per cent) gained, 31 (37.3 per cent) lost and 1 (1.2 per cent) remained unchanged. Estimating progress from gain in weight alone the factor of error is considerable, *viz.*, 61.4 per cent in the unimproved group and 20.9 per cent in the closure group. An interesting finding was that the greatest percentage of cases above

* To be published.

standard on admission was in the group finally classified as unimproved. This shows that being overweight at start of treatment is not an index of subsequent progress.

Toxemia. As indicated in the introduction, temperature reaction was recorded on admission and subsequently in each case. The percentage of cases febrile on admission in the various groups of our classification was: spontaneous closure, 18 per cent; much improved, 23 per cent; slightly improved, 48 per cent; unimproved, 52 per cent; early collapse, 85 per cent. There was a striking parallel between these figures and the percentage of cases with heavy infiltration in the various groups. The high incidence of fever in the early collapse group was one of the chief reasons why a preliminary period of observation was eliminated in that group.

Complications. Tuberculous complications had an increasing incidence as the final status was more unfavorable, ranging from 6 per cent for the spontaneous closure group to 30 per cent for the unimproved group. There was no such correlation in the incidence of nontuberculous complications. Twenty-one per cent of the 296 cases had tuberculous and 5 per cent nontuberculous complications.

Treatment. In recording the kind of treatment received, it was of interest to note that the average duration of bed rest paralleled the severity of the disease (3.6 months in the closure group to 10.1 in the unimproved group). The influence of prolonged bed rest in securing healing could not be accurately determined because there are no controls. In individual cases, as the study was made, significant episodes were observed which tended strongly to strengthen our impression of the importance of adequate initial bed rest. The average duration of bed rest for the early collapse group (7 months) was about twice that of the spontaneous closure group.

Sputum. The fluctuations in the amount and bacillary content of the sputum were found important in individual cases, but were factors difficult to generalize. They are usually proportional to the severity of the disease, but not infrequently there may be little secretion from a large cavity or the patient may be swallowing the sputum, while associated with a small cavity there may be considerable expectoration, either because the patient is sputum conscious, or because there is a secondary complication, as chronic sinusitis. Average figures for 2 by 2 cm. cavities in the closure and unimproved groups were: 10 gm. of Gaffky III (average 1 bacillus in each microscopic field) and 15 gm. of Gaffky IV (average 2 to 3 bacilli in each field), respectively. For 4 by 4 cm. cavities, corresponding figures were: 10 gm. of Gaffky IV and 16 gm. of Gaffky IV. It is observed that the average figure gives very little information, even in the order of a trend.

Factors Revealed by Roentgen Ray. Finally, and probably most important, are factors revealed by the Roentgen ray. Of the whole group there were 24 per cent who during observation had Roentgen

ray evidence of extension of their disease. (This figure does not take into account increase in size of cavities already present, but represents new disease.) The spread was commonest on the same side, then both sides, then the opposite side. The percentage of spread of the early collapse group was 25, practically identical with the group as a whole, and here the order of frequency was opposite side, same side, both sides. The incidence shows an increase from 13 per cent for 2 by 2 cm. cavities to 29 per cent for cavities over 4 by 4 cm.

Extent of Excavation. Table 2 shows an analysis of the 296 cases according to total diameter of cavities as revealed by the Roentgen ray. Prognostic information of value is immediately apparent. Where the extent of excavation was not over 2 by 2 cm., 48 per cent of the cases healed spontaneously. With excavation totalling not over 3 by 3 cm., this figure dropped to 21 per cent for the group, while in the other two groups (4 by 4 and over 4 by 4 cm.) the figures were 15 and 7 per cent, respectively. Furthermore, the percentage of unimproved showed increase with the extent of excavation. There was little difference in the 2 by 2 and 3 by 3 cm. groups (20 per cent), but thereafter the figure jumped to 35 per cent. Early collapse therapy was infrequent in cavities up to 2 by 2 cm. (9 per cent), but was indicated two and three times as often in subsequent groups.

TABLE 2.—RESULTS ACCORDING TO EXTENT OF EXCAVATION.

Total diameter of cavities.	Spontaneous closure.		Much improved.		Slightly improved.		Unimproved.		Early collapse therapy.		Totals.
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	
2 by 2 cm. . .	34	48	7	10	9	13	14	20	6	9	70
3 by 3 cm. . .	13	21	11	19	13	20	11	19	12	20	60
4 by 4 cm. . .	10	15	8	12	9	14	22	34	15	23	64
Over 4 by 4 cm.	8	7	12	11	16	15	37	36	29	28	102
Totals . .	65	..	38	..	47	..	84	..	62	..	296

Table 3 shows the results of a study of the total 464 cavities from the point of view of size, location, heaviness of surrounding infiltration and type of cavity wall. It should be pointed out that further subdivision into pathologic types is not indicated. While undoubtedly it is important in any individual case to decide whether we are dealing fundamentally with caseous or fibrous disease, for statistical purposes it seems sufficient to record our findings in the terms indicated in the table.

TABLE 3.—FACTORS INFLUENCING HEALING.

Size of cavity.		Size.	Location.			Surrounding infiltration.			Cavity wall.			
			Peripheral.	Central.	Medial.	Slight.	Moderate.	Heavy.	Thin.	Moderate.	Thick.	Honeycombed.
2 by 2 cm.	Number of cavities .	81	38	34	9	3	41	37	19	11	7	44
	Per cent spont. closure	40	31	52	22	66	51	25	52	36	28	37
3 by 3 cm.	Number of cavities .	78	37	39	2	6	36	36	23	12	2	41
	Per cent spont. closure	20	21	25	0	33	19	17	26	17	0	19
4 by 4 cm.	Number of cavities .	97	55	35	7	9	45	43	40	16	4	37
	Per cent spont. closure	13	16	17	15	22	19	9	20	12	0	8
Over 4 by 4 cm.	Number of cavities .	208	122	77	9	12	56	140	72	30	26	70
	Per cent spont. closure	6	4	6	10	16	14	3	8	3	0	5
	Number of cavities .	464	252	185	27	30	178	256	154	69	39	202
	Per cent spont. closure	17	12	22	15	27	22	9	20	13	5	14

The factors named above are doubtless subject to variation with individual interpretation, but since they were recorded uniformly they may be considered suitable for study. The location of cavity, recorded as peripheral, central or medial, upper, middle, or lower third, was determined by stereoscopic Roentgen rays, by fluoroscopy, or by both methods. Surrounding infiltration was denoted as slight, moderate or heavy. The cavity wall was described as thin, moderately thick, thick or honeycombed. The size of honeycombed cavities was estimated according to the extent of the diseased area involved.

Size of cavity is again shown to be important in healing prognosis. Other things being equal, the location of cavity in the lung definitely influences the chances for spontaneous healing. In cavities of all sizes central location was more favorable than peripheral. A medial location is least frequent, but is seen to be more favorable than peripheral in our series.

The nature of the infiltration surrounding a cavity is an extremely important factor in influencing healing. The table shows clearly that the incidence of healing with slight surrounding infiltration is high, while with heavy infiltration it is very low, and the patient is likely to be in the unimproved group. The incidence with moderate surrounding infiltration is higher than midway between the two extremes.

Furthermore, as has been frequently recognized, the type of cavity wall has prognostic significance. It is demonstrated in Table 3 that cavities described as having a thin wall have the best chance for spontaneous healing, while those with a moderate wall have 35 per cent less chance. Cavities with definitely thick wall

do very poorly, and in such cavities over 2 by 2 cm. spontaneous healing was not recorded. Honeycombed cavities occupy an intermediate position, but in general their prognosis was below the average for the group. It is difficult to determine closure satisfactorily in this type of cavity, for not infrequently changes interpreted as honeycombing, which may possibly be due to emphysematous blebs, will still be present on the Roentgen ray after the sputum is negative on concentration.

Comment. From the above findings the necessity for individualization in the treatment of pulmonary tuberculosis with cavity is demonstrated. The presence of cavity undoubtedly constitutes a serious menace, but before instituting collapse therapy all factors should be carefully weighed; and if they are not highly unfavorable, a preliminary period of observation with the patient at bed rest is fully justified. The danger of spread of the disease during such a period has, except in acute cases, been overemphasized. In this study, of those who had extension of their disease 85 per cent were febrile at the time of spread. From this it may be inferred that, if the patient is afebrile and doing well clinically at bed rest, there is not much danger of spread. Furthermore, collapse therapy does not eliminate this danger, as is shown by the fact that the early collapse group had a 25 per cent incidence of spread after collapse, as compared with 24 per cent for the group as a whole, which contained many hopeless cases. If it is apparent that spontaneous healing is taking place, the bed rest program should be continued with fluoroscopic examination at intervals of not longer than 2 weeks and Roentgen rays at intervals of not longer than 1 to 2 months. If these observations do not reveal satisfactory progress, collapse therapy is indicated. As to the likelihood of the development of obstructive and troublesome adhesions between the layers of the pleura during the preliminary period, there is no positive evidence that such is the case. It is rather the type and distribution of the lesion with involvement of the pleura and not necessarily the duration of the disease which determines whether adhesions will be present. Packard⁶ has shown that a good collapse by pneumothorax may at times be brought about in cases of long standing with extensive retraction. At Loomis, several instances have been observed in which there developed, apparently simultaneously with acute extension, surface adhesions directly over and limited to the newly involved area. Without denying the value of collapse therapy there are a number of reasons why spontaneous healing, when it can be obtained, is the most desirable form of healing. First, there is the time element. In this series the average time for spontaneous closure was 5 to 6 months. According to Herben and Franklin, the average time for closure by pneumothorax in cases where this desirable result was brought about was 5 to 6 months; and it must be remembered that this is merely the starting

point, for the lung must usually be kept down at least 2 years and then reëxpanded. Furthermore, the average duration of sanatorium residence for the early collapse group was $11\frac{1}{2}$ months, compared with $10\frac{1}{2}$ months for the spontaneous closure group, and the average period of bed rest for these groups was 7 months and $3\frac{1}{2}$ months, respectively. In addition, collapse therapy is not without its risks. In prescribing pneumothorax, the fact is frequently overlooked that complications are the rule rather than the exception. Tuberculous pleuritis complicating therapeutic pneumothorax is very frequent; this is at times so severe as to cause, by reason of pleural thickening and ingrowth of fibrous tissue from the pleura, permanent loss of function of the lung, and necessitate thoracoplasty. In the average pneumothorax case the damage to the lung is out of proportion to the extent of the disease, and marked retraction on reëxpansion is frequent. That these objections, however, did not, in our estimation, constitute contraindications, especially when the disease failed to heal or was progressive, is shown by the fact that 49 per cent of the 296 cases received some form or combination of forms of collapse therapy during residence.

Summary. A study of 296 cases of pulmonary tuberculosis with cavity (464 cavities) at Loomis Sanatorium showed the following: Classified as to extent of excavation, there were 23.6 per cent with cavity, 2 by 2 cm.; 20.1 per cent, 3 by 3 cm.; 21.6 per cent, 4 by 4 cm., and 34.4 per cent over 4 by 4 cm. Of the whole group 22 per cent secured spontaneous closure of cavity. The chance for spontaneous healing was inversely proportional to the size of the cavity. Closure occurred in 40 per cent of 2 by 2 cm. cavities, 20 per cent of 3 by 3, 13 per cent of 4 by 4, and 6 per cent of over 4 by 4.

Where the infiltration surrounding the cavity was slight, the percentage of spontaneous closure was higher for cavities of all sizes. The heavier the surrounding infiltration the less the chance for closure to a minimum of less than half the average for cavities with heavy surrounding infiltration. Similar relations pertain in considering the thickness of the cavity wall: thin-walled cavities of all sizes, especially with slight surrounding infiltration, do better than the average. The thicker the wall the poorer the chance for healing to a minimum of 5 per cent for thick-walled cavities.

Central location gives twice as good a healing prognosis as peripheral, that is, close to the parietal pleura. Right-sided cavities in this series had twice the percentage of spontaneous closure of left-sided and three times that of bilateral cavities.

The age group 15 to 25 did only about 50 to 75 per cent as well as the average in spontaneous healing, and had a large number unimproved (45 per cent *versus* 25 per cent average). In girls aged under 20 years only about half (11 per cent) the average secured spontaneous closure and the per cent unimproved was 64. Over 45 years there was a high percentage unimproved (40 per cent).

Gain in body weight is shown to be an unreliable index of healing, since 60 per cent of the unimproved gained weight.

The incidence of spread for the whole group, which included many hopeless cases, was 24 per cent. In the early collapse therapy group, the incidence of spread was the same.

Classification made on the basis of spontaneous healing (except for 22 per cent in the early collapse therapy group) showed 22 per cent spontaneous closure, 13 per cent much improved (cavity reduced to a remnant; sputum positive or negative), 15 per cent slightly improved, and 28 per cent unimproved.

Sixty-five per cent of the unimproved, 50 per cent of the slightly improved and 7 per cent of the much improved received collapse therapy. All of these constituted 27 per cent of the 296 cases. Thus, a total of 49 per cent of the group received some form or combination of forms of collapse therapy, and roughly one-third, or 17 per cent, secured cavity closure thereby.

Finally, using all forms of treatment in 296 cases with cavity, an excellent result was obtained in 39 per cent (closure), and a good result in an additional 25 per cent (much improved).

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INCIDENCE OF RHEUMATIC FEVER IN NEW YORK CITY HOSPITALS.*

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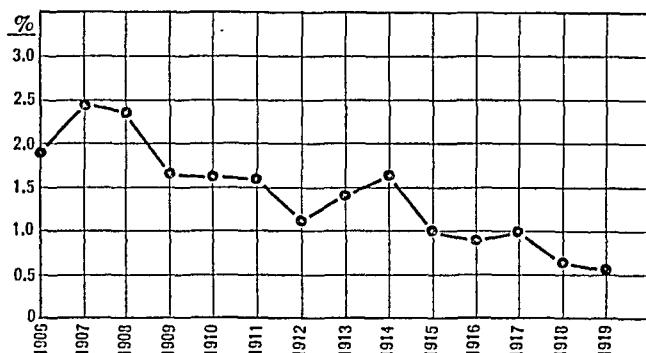
It has been noted by a number of physicians that there were fewer cases of rheumatic fever on the wards in the general hospitals after the World War than there had been previously. The present survey was undertaken to determine the truth of this statement as well as the underlying cause. It was hoped to obtain some information concerning the incidence of the disease and the effect of various conditions, such as the removal of infection, on the morbidity of rheumatic fever in this city.

Such an investigation is necessarily fraught with many difficulties and inaccuracies. The change of fashion as to what constitutes

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a diagnosis of acute rheumatic fever, the ever changing house staff and attending staff, and the incompleteness of records in the early days, are some of the points which must be considered before reaching a conclusion. In order to minimize the errors due to the first difficulty, *i. e.*, the difference in terminology of diagnosis, the charts of all the cases diagnosed as acute rheumatic fever, acute polyarthritis and acute arthritis have been examined. Only those cases were included in this series which had fever and an inflammatory arthritis affecting two or more large joints and usually showing cardiac manifestations. It was also thought that limiting the study to two hospitals, where the respective attending staffs had been present for a rather long period, would further minimize this difficulty.

Similar studies have already been reported by many other investigators, but the results are not in agreement. Alexander Lambert¹ published a paper in 1920 on the incidence of acute rheumatic fever

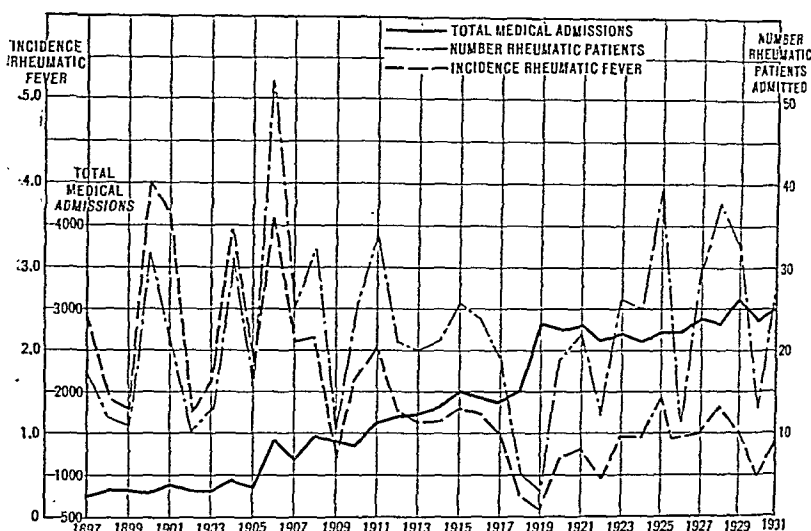


GRAPH 1.—Incidence of acute rheumatic fever.

at Bellevue Hospital. He reviewed the data of the cases from 1906 to 1919 and called attention to the steady decline in the number of cases. This decline, which is illustrated in Graph 1, was attributed by Lambert to the increasing removal of foci of infection, particularly due to the prevalence of better dental hygiene.

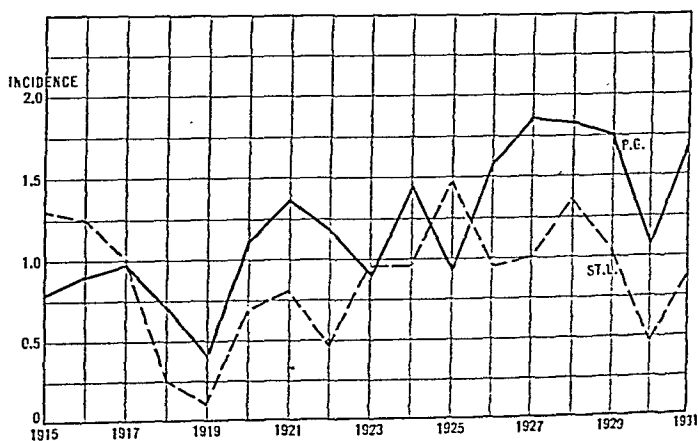
Poynton² began his book, "Recent Advances in the Study of Rheumatism" (1931) by saying "rheumatic fever in the clinical form would seem to be on the wane." On the other hand, in 1924 Ingerman and Wilson³ concluded a paper by stating that "the general progress in preventative medicine and hygiene in the last twenty-five years has not seemed to influence the clinical course of rheumatism as we see it today." The latter investigators studied 185 cases of rheumatic fever, 88 per cent of which had their tonsils removed. Recurrences of rheumatic manifestations were observed in 75 per cent of the tonsillectomized patients in from 1 to 11 years. In the control group of 97 cases studied over a similar period, 80 per cent showed recurrence of rheumatic manifestations.

Kaiser,⁴ however, throws a ray of hope into that dark outlook. In his investigation, 48,000 school children were divided into two groups; 20,000 who had had their tonsils removed at least 5 years



GRAPH 2.—Acute rheumatic fever (St. Luke's Hospital).

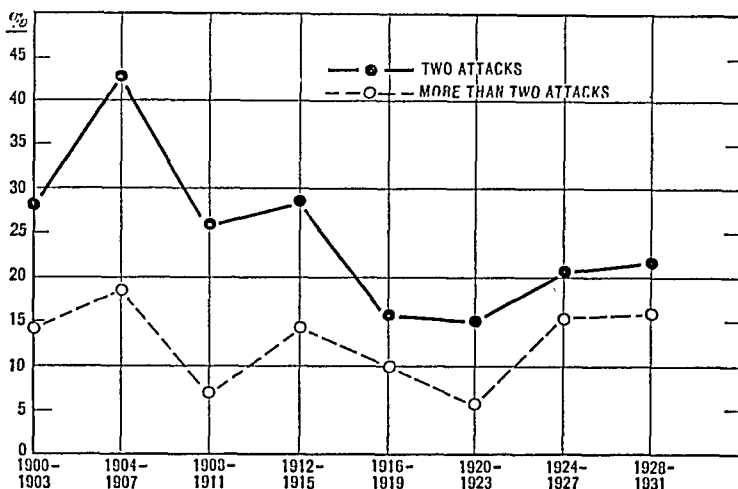
previously and 28,000 upon whom the operation had not been performed. At first sight the incidence of rheumatism did not seem



GRAPH 3.—Incidence of acute rheumatic fever (Post-Graduate and St. Luke's Hospitals).

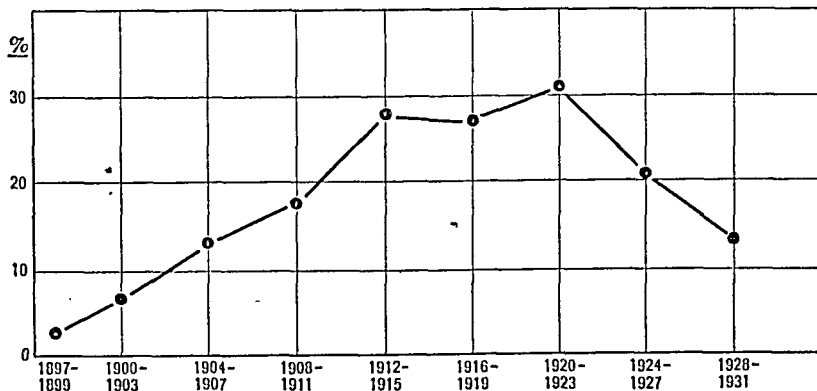
to be much influenced by the operation, since it occurred in 8 per cent of the tonsillectomized children and in 10 per cent of the non-tonsillectomized. Recurrent attacks of rheumatic fever, however,

were decidedly less common in the group who had had their tonsils removed and the incidence of carditis following chorea was also definitely diminished.



GRAPH 4.—Incidence of recurrent attacks (St. Luke's Hospital).

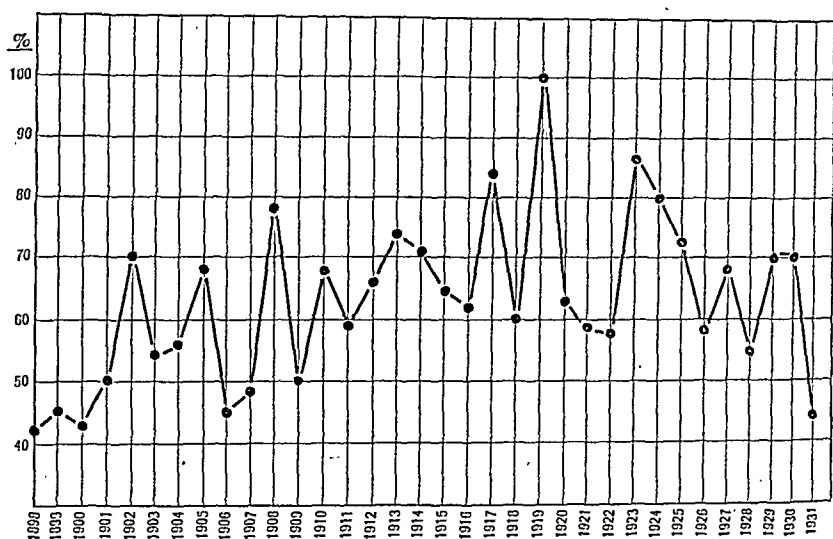
Of the 20,000 tonsillectomized children, 450 were suffering from rheumatic heart disease, while 817 were similarly affected among the 28,000 who still retained their tonsils. More significant was the discovery that in 478 cases of carditis the condition had developed in 83 per cent before operation, whereas it appeared as a first manifestation after enucleation of tonsils in only 179.



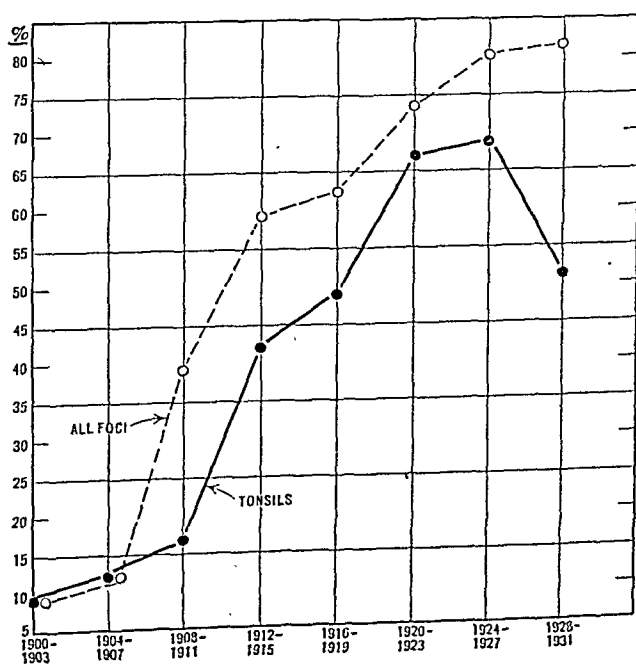
GRAPH 5.—Incidence of acute rheumatic fever with temperature of 104° F. or higher (St. Luke's Hospital).

It is unnecessary to make an extended survey of the literature here. Suffice it to say that the expressed opinion on the question of the incidence of rheumatic fever is varied and contradictory. This is at least partly due to the incomplete statistical analyses which have served as their basis.

In the present series the records of 787 cases of acute rheumatic fever at St. Luke's Hospital and of 365 cases at the New York Post-Graduate Hospital have been studied. Since 1898 there have been

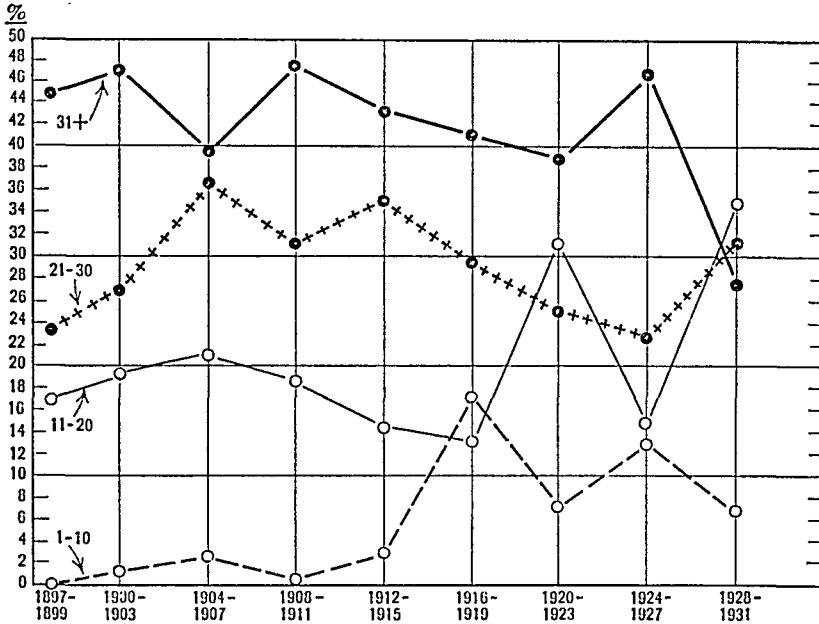


GRAPH 6.—Incidence of cardiac disease in acute rheumatic fever (St. Luke's Hospital).



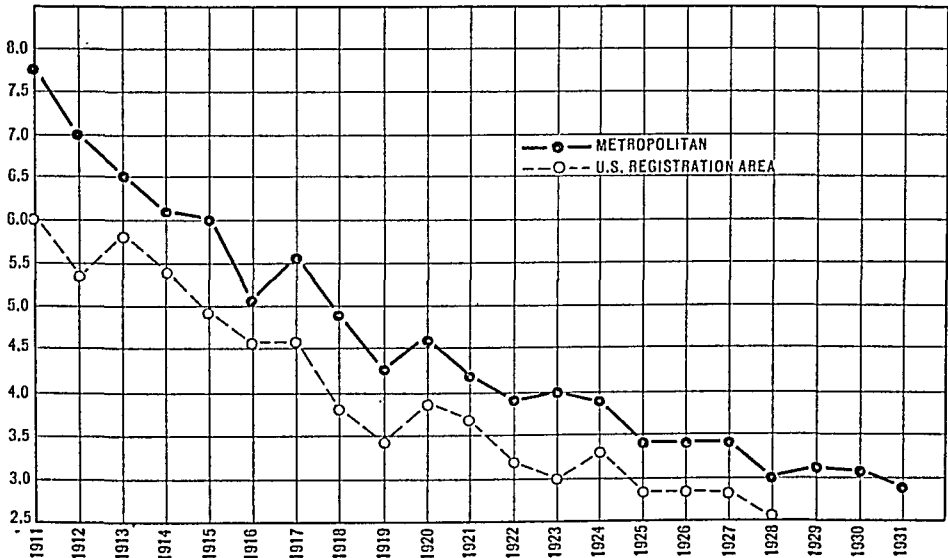
GRAPH 7.—Incidence of focal infection (St. Luke's Hospital).

wide fluctuations in the number of admissions of patients with rheumatic fever to the two hospitals under investigation. In spite



GRAPH 8.—Incidence of rheumatic fever according to age (St. Luke's Hospital).

of the variable incidence there appears to have been a steady decline both in the absolute number of admissions of rheumatic fever

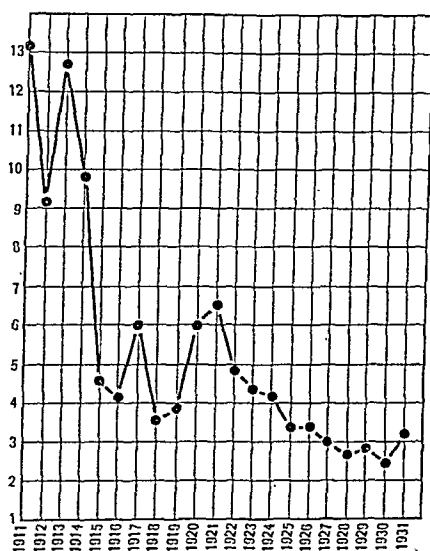


GRAPH 9.—Death rates per 100,000 from acute rheumatic fever.

cases and in the relative number, *i. e.*, as compared with other diseases. This condition lasted until 1919, since when there has

been a slow increase in both absolute and relative number of admissions. Graph 2 shows the incidence of acute rheumatic fever at St. Luke's Hospital from 1897 to 1931: On this graph is also plotted the annual number of medical admissions and the actual number of rheumatic fever admissions. Graph 3 indicates the incidence of acute rheumatic fever at St. Luke's and New York Post-Graduate Hospitals, located in different parts of New York City. The similarity of these curves suggests that a study made in either of these hospitals might give a fair idea of the average occurrence of the disease in this city.

Although the disease still occurs in a severe form, recurrences are less liable to occur now than formerly (Graph 4). In studying the charts of the earlier years, however, one is impressed by the rela-



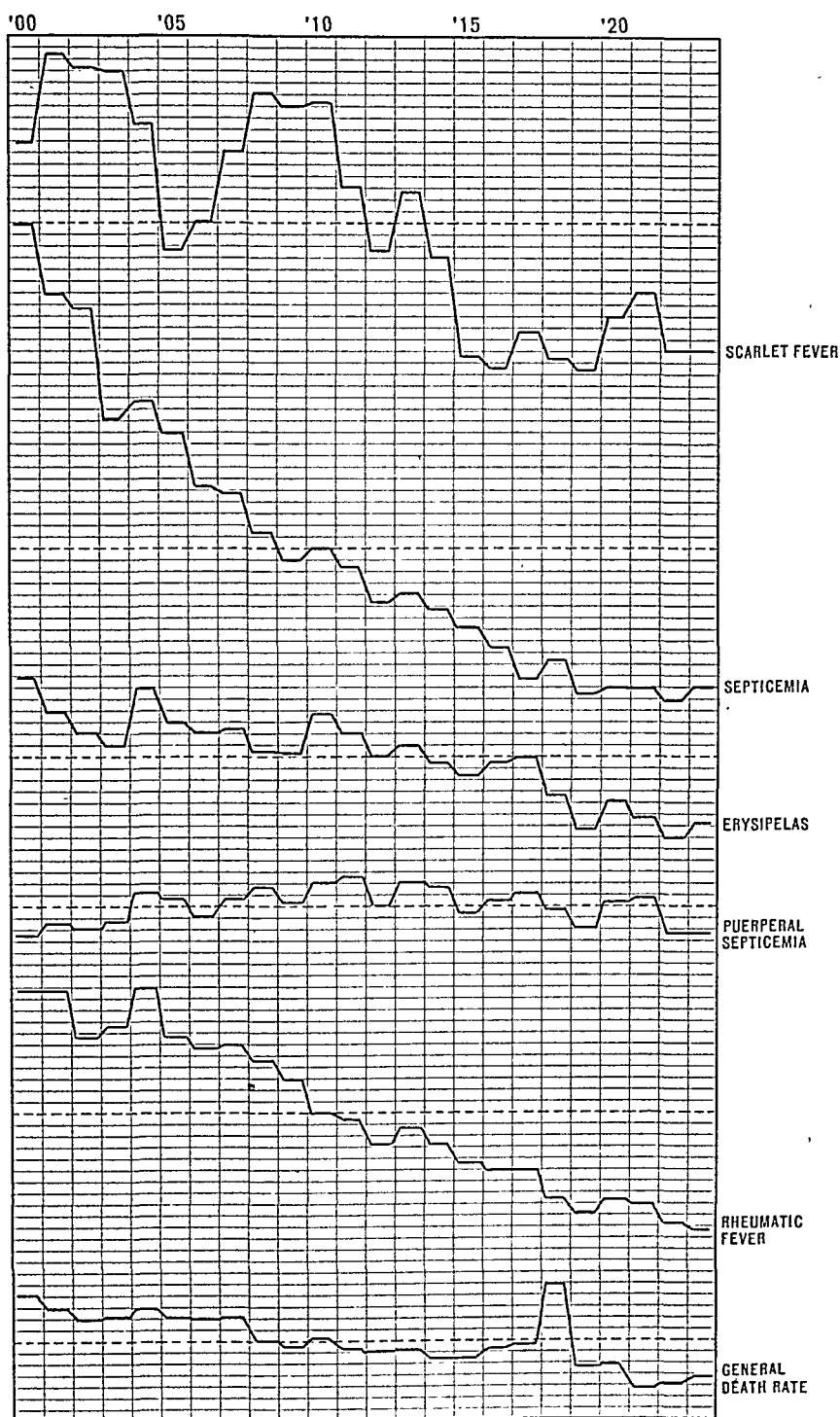
GRAPH 10.—Death rate from scarlet fever.

tively greater intensity as evidenced by the complication of pericarditis and the number of patients in whom the temperature rose above 104° . It is apparent from Graph 5 that there was a steady increase in the percentage of cases in which the temperature was 104° or greater until about 1923. In the last 6 years there has been a definite fall.

Graph 6 presents the curve for the incidence of carditis in acute rheumatic fever. It fluctuates considerably, but shows on the whole a tendency to rise until about 1919. After that there is a drop in the general slope of the curve. The graph for the cases from the New York Post-Graduate Hospital is again similar to that for St. Luke's, so we have not reproduced it here.

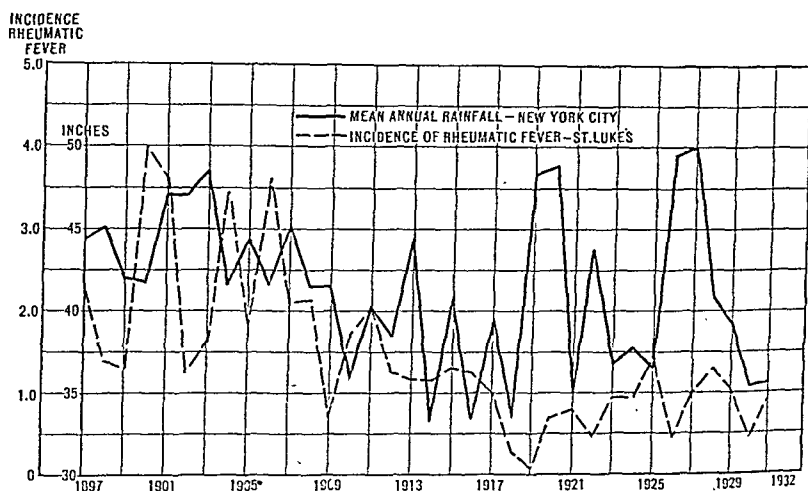
It is obviously impossible to take into account all the conditions

affecting the incidence of the disease, but four possible points suggest themselves as being of primary significance.



GRAPH 11.—A comparison of the death rates in the U. S. Registration Area from scarlet fever, septicemia, erysipelas, puerperal septicemia and rheumatic fever for the period 1900-1923.

FIRST. *The Problem of Removal of Foci.* There has been an increasing tendency in recent years to look for and remove foci of infection. Graph 7 shows the great increase of foci found and removed at St. Luke's Hospital since 1900. If the presence of foci is an important factor in the general susceptibility to rheumatic fever, then one might expect a graph for the frequency of this disease to be the reverse of that for foci found and removed, with a lag of several years in the former. In other words, a great increase in the detection and treatment of foci would be reflected several years later in a decreased incidence of rheumatic fever. But when Graphs 2 and 7 are compared we find a gradual decrease, with fluctuations, in the incidence of rheumatic fever until 1919, with a coincident steady rise in the removal of foci. This rise continues, but the inci-



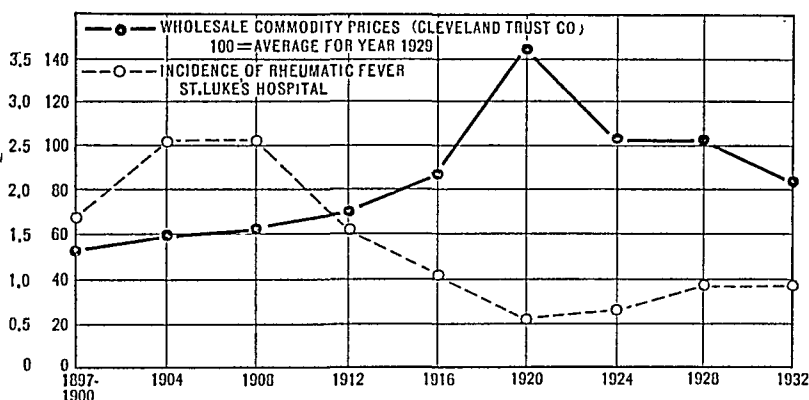
GRAPH 12.—Relation of moisture to rheumatic fever.

dence of rheumatic fever also increases. Although there has been a recent drop in the frequency of tonsillectomies, it cannot be held responsible for the increase in rheumatic fever, because this increase began before the drop in tonsillectomies. Our graphs, then, do not permit us to conclude that the removal of foci of infection has any significant effect on the incidence of rheumatic fever.

The variations in the number of cases of rheumatic fever in the different age groups have been presented in Graph 8. The patients were divided into four groups: 1 to 10 years, 11 to 20, 21 to 30, and 31 and over. Inspection of the curves leads to the conclusion that in the older groups the disease shows a greater tendency to decrease in recent years than in the younger groups. This might possibly indicate that the older people are now deriving some benefit from

removal of foci at earlier ages, except that we have seen from Graph 7 that the relation of the presence of foci to rheumatic fever is very doubtful.

SECOND. *The Possible Cyclical Character of Rheumatic Fever.* It has been said that rheumatic fever follows a cycle similar to that found in many acute infectious diseases. The rapid fall in the mortality of acute rheumatic fever from 1911 to the present is seen in Graph 9. These curves were supplied by Mr. Van Buren, statistician of the Metropolitan Life Insurance Company. Not only is there a rapid fall in the mortality, but the curve may be considered to be made up of four fairly similar cycles of 3 to 5 years each, characterized by a sharp rise and subsequent gradual and more prolonged fall. Graph 10 shows a fairly similar mortality curve for scarlet fever. Whether the similarity of the curves indicates a changing degree of virulence of the infection or whether it indicates improving hygienic conditions which are reflected in decreasing susceptibility



GRAPH 13.—American business activity.

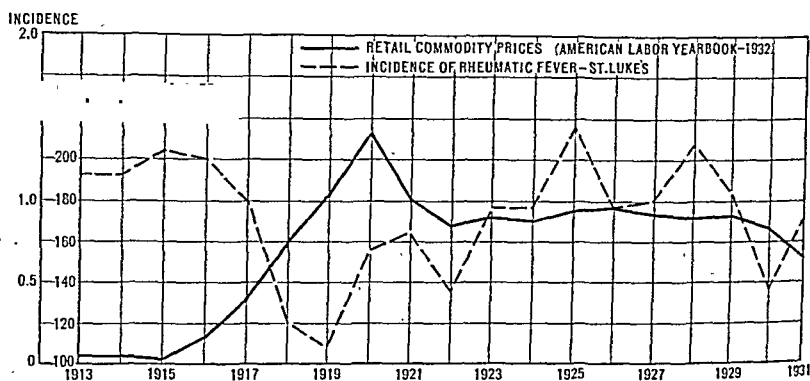
to infection is difficult to say with the data at hand. It is equally probable that the changes in mortality of the two diseases do not have a similar cause at all.

Graph 11 is reproduced from a paper published by Atwater⁵ in 1927 on the epidemiology of acute rheumatic fever and related diseases in the United States based on mortality statistics and covering the period 1900 to 1923. He concluded that the history of the disease in the United States during the past half century showed a striking decline in the number of deaths and probably in the number of cases as well. The graph shows the parallelism between the proportion of deaths due to rheumatic fever and to streptococcal diseases, and the apparent cyclic character of these diseases.

THIRD. *The Question of Rainfall.* The disease is more prevalent in periods of greater rainfall. It is well known that rheumatic

fever is a disease of cold, damp countries, occurring mostly along the coast, river bottoms and canals. This fact suggests that years of increased rainfall might be marked by an increase in the incidence of acute rheumatic fever. This relationship is shown in Graph 12. The average annual rainfall was taken from the figures of the weather bureau in New York City.⁶

If it is true that rheumatic fever is more liable to occur in wet weather, then a rise in the rainfall curve ought to be accompanied by the curve for the incidence of rheumatic fever within the following year. When we examined the rheumatic fever curve after the seven rainiest years, we found a rise in 6 instances, whereas after the 7 driest year there was a subsequent drop in 4 instances, a rise in 2 and no change in 1. It seems justifiable to draw the conclusion that wet weather is one of the factors increasing the prevalence of rheumatic fever. In contradiction to this conclusion, Newsholme⁷



GRAPH 14.—American business activity.

has reported that in England there is an increase in rheumatic fever in dry years, and he attributed this to the increase in the amount of dust and the consequent greater ease of spreading infections.

FOURTH. *The Question of Economic Status.* Acute rheumatic fever seems to be a disease of the poorer classes and would therefore be more liable to be widespread at times when more people are deprived of adequate food, clothing, fresh air and medical attention. It is almost impossible to choose a satisfactory index for the general cross-sectional economic welfare of the inhabitants of New York City. Since there are no reliable statistics on the number of unemployed, it would be very inaccurate to use average weekly earnings. The income tax report is likewise unsatisfactory because it gives no idea of the economic fluctuations of the large group who do not pay a tax and with which we are mainly concerned. In

this study we have first plotted the curves for the wholesale commodity prices (Graph 13), which give a fairly good index of business activity. Graph 14 shows the fluctuations in the average retail prices of 30 basic commodities, and from this some idea of the variation in the cost of living can be gained. In both these graphs the important points to be observed are the rise in economic activity until 1920 which was followed by a sharp fall and the next period of stability which was broken by the crash of 1929. If we attempt to correlate with this the curve for the incidence of rheumatic fever we find that a fairly good reciprocal relationship manifests itself in Graph 13. In the more detailed graph (Graph 14), the correlation is not so uniform. It is true that the incidence drops during the first period of "prosperity," but it had already begun to rise before the 1920 depression was well under way. Inspection of the graph reveals other definite discrepancies and, on the whole, hardly seems to lead to the conclusion that fluctuations in economic welfare and the morbidity of rheumatic fever go hand in hand. The statistics for this year, however, will be interesting in this connection because of the sharp rise in unemployment and distress in the lower middle class group.

Summary. 1. There has been a decline in the incidence of acute rheumatic fever at both St. Luke's Hospital, New York and the New York Post-Graduate Hospital from 1897 to 1919 and a rise since that time.

2. Four possible factors have been discussed with reference to this changing incidence: (a) Removal of foci of infection; (b) Cycles in the virulence of infectious diseases; (c) Rainfall; (d) General economic conditions.

The author wishes to express his appreciation to Dr. Lewis F. Frissell who suggested this survey and to Dr. Walter Lough for his suggestions and help.

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GASTRITIS IN ITS RELATION TO OTHER DISEASES.*

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GASTRITIS, which may be defined broadly as a diffuse degenerative or inflammatory disease of the mucosa of the stomach, was looked upon during the latter part of the past century as the common cause of indigestion and responsible for many other ills of the body. With the discovery that the microscopic mucosal changes described by the pathologists of that time were due to postmortem autolysis and with the coincident popularization of the stomach tube, attention gradually shifted to the secretory disturbances of the stomach. Even the advanced types of chronic gastritis, recognizable by gross atrophic and hypertrophic changes, lost their interest for the pathologist and clinician, and for a time no attempt at correlation of the anatomic and secretory alterations was made. Although Faber and Lange,¹ in 1908, making use of a technique introduced 18 years before by Hayem for prompt fixation of the gastric wall at death, described minute inflammatory changes of the stomach mucosa that were associated with achylia, their work attracted relatively little immediate attention. This was probably due, in part, to the fact that at the same time gastric ulcer, gall bladder disease, and appendicitis were being recognized as frequent causes of indigestion. Even now, in spite of the great interest in the gastric secretory disturbance demonstrated by Castle² as responsible for Addisonian anemia, some of the textbooks on pathology entirely neglect the subject of gastritis, and at most autopsies only a brief note on the gross appearance of the stomach is made.

Faber,³ however, has continued to emphasize the significance of gastric inflammatory changes in relation to disturbances of stomach secretion. He considers that a mild or localized gastritis may exist with the acid secretion intact or even increased, while any diffuse form, especially that with advanced glandular atrophy, leads to a marked reduction or absence of such secretion. Orator⁴ and Konjetzny,⁵ basing their work chiefly on the study of resected specimens, have arrived at much the same conclusions. Hurst,⁶ who like Conner⁷ and Wilkinson⁸ believes in an hereditary or constitutional factor in the development of achlorhydria in some instances, insists that it is usually explainable on the basis of a gastritis. He has demonstrated that often a recovery of acid secretion may be

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obtained by hydrogen peroxid lavage, even occasionally when the histamin test has been negative, and considers this as strong evidence in favor of the gastritis being primary. He has observed cases of pernicious anemia with achlorhydria in which the onset of symptoms dated from an acute gastritis. Additional support for the contention that gastritis leads to a loss of acid secretion is found in the rising incidence of achlorhydria with age. A lack of mucus in the gastric contents, which usually is present with achlorhydria, does not eliminate gastritis as the causative factor, because in the advanced atrophic stage no secretion whatever may be possible. Finally, from the clinical viewpoint, I have observed many cases of achlorhydria in which roentgenologic study showed the typical signs of hypertrophic gastritis.

From the point of view of the pathology involved it may be said that while those especially qualified to speak, such as Faber, Konjetzny, Orator, and Hillenbrand,⁹ are by no means in entire agreement as to the anatomic criteria which separate the borderline cases into normal and abnormal groups for certain age periods, it does seem clear from their investigations that a so-called chronic gastritis consisting of an extensive glandular atrophy, often with gland change to the type of the small intestine, an increase in follicular centers, round cell infiltration between the glands, and eventually destruction of the glandular structures with overgrowth of fibrous tissue frequently occurs, particularly in persons past middle life. These changes may be present in either of the gross types of chronic gastritis, usually referred to as hypertrophic and atrophic.

My interest, aroused in this subject some years ago, has been intensified by Castle's researches and Hurst's clinical observations. For 2 years W. O. Abbott, of our clinic, has been injecting with formalin solution the stomachs of patients dying in our wards and securing specimens from such of them as came to autopsy; these, with resected specimens obtained at the operating table, he has subjected to careful microscopic study. His work will be reported in detail separately, but I may say here that it tends to support the contention that chronic gastritis and achlorhydria are usually associated.

Although it is still impossible to state with certainty which is primary, the gastritis or the secretory dysfunction, the mere fact of their common association justifies consideration of chronic gastritis in its relation to some of the other diseases in which achlorhydria is usually found. These are Addisonian anemia, other anemias of the chlorotic or microcytic type, subacute combined degeneration of the spinal cord, carcinoma of the stomach; sometimes diarrheal diseases, such as sprue; less frequently diseases of the gall bladder, arthritis, etc. The achlorhydria itself has not been proved to be of etiologic significance in any of these diseases, but it is reasonable to assume that the lack of hydrochloric acid

may be only one evidence of an altered mucosa, and that other associated disturbances, such as a lack of the intrinsic factor of Castle in Addisonian anemia, may be on a similar organic basis.

Relationship to Other Diseases. Since, then, a so-called chronic gastritis, consisting of more or less diffuse degenerative and inflammatory changes, and usually characterized clinically by a hypochlorhydria or an achlorhydria, is recognized, we are prepared to consider in relation to this disease of the stomach some of the other diseases with which achlorhydria is commonly associated. I shall refer at this time to only two of them: gastric carcinoma and Addisonian anemia.

(A) *Gastric Carcinoma.* With the exception of the cases that are secondary to ulcer (probably not more than 10 per cent) and those that are secondary to benign polyp (probably not more than 5 per cent) we have had in the past no very clear conception regarding the predisposing factors in the production of gastric cancer. For the majority group, however, including those on a polyp basis, and in definite contrast with those on an ulcer basis, two clinical facts stand out prominently: (1) that they usually present no pre-cancer symptoms, and (2) that an achlorhydria is commonly present. The absence of a previous gastric history has been responsible for the idea, still in vogue, that this type of carcinoma springs *de novo* from a normal gastric wall, but the associated achlorhydria is not consistent with such a theory. This becomes manifest when attention is directed to the following considerations:

1. The patients who are believed to have developed cancer on a stomach ulcer basis show no progressive decrease in gastric acidity, this indicating that the achlorhydria is not a secondary development. We have usually found free acid in our cases that gave a long ulcer history, no matter what the stage of the malignant process. Hurst had 3 such cases followed for a considerable period of time, and found no decrease in the acidity; he has not seen a case in which acid was once present and later in the disease disappeared. In 12 of 14 ulcer-cancer cases reported by Orator,⁴ and in 9 cases reported by Stewart¹⁰ in which acid was at one time present, it persisted to the end. Polland and Bloomfield¹¹ report 2 ulcer cases in which the acidity was higher after the secondary development of cancer.

2. On the other hand, the achlorhydria usually found in the majority group, those with a short history and nothing to suggest a preceding ulcer, has been demonstrated in a few cases before the development of cancer. Hurst⁶ has cited a case that had achlorhydria 2 years before the development of recognizable cancer; Alexander,¹² 1 with achlorhydria 26 months before; Veale,¹³ 1, 3 years before; Porges,¹⁴ several, for years before. The scarcity of such reports is not surprising since gastric analyses are rarely done on patients without gastric symptoms.

Furthermore, it is now appreciated that carcinoma of the stomach not infrequently develops in patients the subject of Addisonian anemia, such patients almost always having had an achlorhydria for a long time. We have had at least 3 instances of gastric cancer in pernicious anemia cases, and Hurst⁶ has reported 5 such cases. In 1 of his cases the carcinoma developed 9 years after onset of the anemia and 4 years after its cure by the use of liver. In this case a partial gastrectomy was done and a section from the unaffected fundal portion of the stomach was removed for study: this showed atrophic glandular changes. Hurst has also referred to the relatively high incidence of carcinoma of the stomach and of pernicious anemia in different members of the same family. The age and sex incidence for the two diseases is also much the same.

3. The prognosis after operation in the gastric cancer cases with free hydrochloric acid is no better, in fact not so good, as in those with achlorhydria. This is our own impression, is confirmed by Hurst, and is the experience of other clinicians. It would be the reverse if the achlorhydria were a secondary development and so indicative of more advanced malignant change.

Thus, it seems clear that the achlorhydria present in the majority of cancer of the stomach cases cannot be attributed to the cancer itself. Since, however, we have presented evidence to indicate that such achlorhydria is usually associated with chronic gastritis and that such gastritis ordinarily gives rise to no symptoms, an antecedent gastritis may be considered as an explanation for the lack of hydrochloric acid.

In this connection our reference to the fundus specimen secured by Hurst in a case of pyloric cancer, and which showed atrophic changes, assumes significance. Furthermore, Konjetzny and Salzman⁵ have showed histologic transitions from chronic gastritis to cancer. According to Bloomfield and Pollard,¹⁵ Lebert, in 1878, found in 41 of 56 cancer cases an extensive gastritis, even at a distance from the growth, and was the first to point out the relationship. Orator,⁴ by more modern methods, has demonstrated to his satisfaction such a lesion in 19 of 20 so-called "primary" carcinomatous cases, whereas in ulcer-cancer such gastritis as he found was localized about the malignant lesion only, usually in the pyloric end of the stomach, and did not involve the fundus.

Abbott, of our clinic, has had in his series of stomach specimens 11 from cases of gastric cancer: in 4 an achlorhydria had been demonstrated by fractional or histamin test; in 3, the free acid was within normal limits, and in 4 no gastric analysis had been made. Of the 4 with achlorhydria all gave a short history, averaging 8 months; while the duration of digestive symptoms in the 3 cases with acid was respectively 13 months, 5 years, and 42 years. In only 2 of the cases, both with achlorhydria, did he have the entire stomach, and in both of these an extensive atrophic gastritis

was present; the others, including those with free acid, also showed atrophic or hypertrophic gastritis, but only the parts of the stomach near the malignant lesion were available for study.

Eliason and the author¹⁶ found evidence of gastritis, usually hypertrophic, in our 8 cases of polyp-cancer, though in some instances the malignancy was just beginning: in all of them an achlorhydria was present.

Thus certain data are available to indicate that a gastritis, responsible for achlorhydria, has preceded some cases of gastric cancer, and probably such a lesion, unrecognized, has been present in many more.

(B) *Addisonian Anemia*. Equally interesting is the consideration of primary pernicious or Addisonian anemia in connection with gastritis. Even before the demonstration by Cahn and von Mering¹⁷ in 1886, that achlorhydria was usually associated with this type of anemia, atrophic changes in the gastric mucosa were demonstrated by Fenwick¹⁸ in this disease. He, together, with Quinke, Nothnagel and Ewald, who also called attention to the relationship, regarded the gastritis as primary. The earlier references to the stomach alterations must now be disregarded, however, due to doubt concerning postmortem effects; but, in 1900, Faber and Bloch,¹⁹ using an acceptable technique, described extensive changes in the gastric mucosa of 2 patients dying of this disease: a diffuse inflammation leading to destruction and atrophy of the glands, most severe in the cardia and decreasing toward the pylorus. They were inclined to believe, at that time, that the gastric affection and the blood changes were in common due to a toxic or infectious cause.

Herzberg,²⁰ in 1911, after a very careful study of the stomachs of primary anemia cases, in many of which she found a severe atrophy of the mucosa, inferred that it was improbable that the gastritis was primary. She admitted, however, that the gastric changes often were found in the early stage of the anemia, and found no such changes in the secondary anemias. She also believed that the gastric and blood changes were due to the same cause.

It is probable, unless it becomes possible to produce pernicious anemia experimentally, that a determination as to which, the anemia or the gastritis, is primary can never be made on purely pathologic-anatomic grounds. Sections from the stomachs of persons who later develop pernicious anemia are not likely to become available for microscopic study. On a clinical basis, however, we now have reason to believe that the gastritis appears first.

This conclusion is based, in the first place, on the observations of many workers that achlorhydria, which certainly is the outstanding clinical sign of gastritis, frequently precedes the development of pernicious anemia. Faber and Gram,²¹ Sturtevant,²² Riley,²³ and Conner⁷ had cases that showed an achlorhydria from 4 to

25 years before the development of pernicious anemia. Moschcowitz²⁴ especially has claimed that because it exists throughout the disease, does not disappear during remissions, and has been found so often to precede the onset of the anemia, the achlorhydria must be looked upon as primary.

Secondly, pernicious anemia not infrequently occurs in persons in whom the diagnosis of chronic gastritis has previously been made. Hurst⁶ refers to its development in 4 patients who were chronic alcoholics, and in 1 of these he observed a return of acid after treatment of the gastritis. In 3 other cases of pernicious anemia, believed to have developed on the basis of a gastritis, he got a return of acid after treatment, this suggesting that the gastritis was not of the completely atrophic type. Torrey²⁵ tells me of 3 of his cases of alcoholic gastritis that late in the disease presented the picture of this type of anemia together with marked cord changes. I have had 1 such case on an alcoholic basis in which a small amount of free acid was demonstrable: the anemia responded readily to liver therapy.

Finally, roentgenologic study sometimes demonstrates an advanced hypertrophic type of gastritis in pernicious anemia cases. In our last 27 cases so studied, 7 showed such marked hypertrophy of the gastric rugæ that it seems impossible that it could have developed within the time that the patients had been anemic.

Similarly suggestive of the primary importance of gastric mucosal changes in Addisonian anemia, and of even more immediate interest, is the clean-cut demonstration by Castle² that the absence of an intrinsic factor, normally secreted by the stomach, causes the disease. Such a secretory disturbance, like the achlorhydria, can most easily be explained on the basis of an anatomic change in the gastric wall.

Conclusions. 1. Chronic gastritis, manifested clinically by a decrease or absence of hydrochloric acid and sometimes by the presence of mucus in the gastric contents, is commonly found in association with carcinoma of the stomach and Addisonian anemia.

2. Evidence is presented to indicate that such gastritis usually precedes the development of these diseases and is a factor in their origin.

3. Since the etiology of chronic gastritis, its various forms and the means of recognizing it clinically are not understood, it is obvious that if we are to prevent its development and the diseases for which it seems to be responsible, much experimental and clinical investigation is clearly indicated.

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THE REDUNDANT DUODENUM.

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ANOMALIES of the duodenum are not infrequently observed in the routine roentgenologic examination of the gastrointestinal tract. In recent years greater attention has been directed to this portion of the bowel, and abnormalities have been commonly noted which have hitherto escaped recognition. Anomalies of the duodenum are much more common than a survey of the literature indicates. Clinically, but little attention has been directed to these conditions up to a comparative short time; but considerable importance is now attached to them especially in regard to their etiologic relationship to the production of digestive symptoms. Recent literature abounds with individual case reports of various anomalies of the duodenum, which have been especially discovered as a result of a more thorough roentgenologic investigation. Such cases are, however, rarely recognized by any other method of examination. Most of these findings cannot be termed as definite clinical entities and the clinical signs of this group are rarely distinctive or characteristic. The diagnosis must necessarily depend upon a painstaking Roentgen study.

Too often, however, these anomalies escape the observation of the

roentgenologist and thus remain undetermined. It is probably true that with better Roentgen technique and more thorough investigations they will become more frequently recognized and their full significance brought to light.

The duodenum, about 10 inches in length, has a definite configuration in the shape of an incomplete circle or C-shaped, which under abnormal conditions may take on bizarre forms, such as the U-shaped, V-shaped and other distortions (Fig. 1).

The first part of the duodenum is the most mobile, but the remaining portions are practically fixed and bound down to adjacent viscera and to the peritoneum. The first portion of the duodenum, the most movable, is more or less fixed by the hepatoduodenal ligament, the free margin of the lesser omentum. A fold of the hepatoduodenal ligament extends down from the posterior surface of the gall bladder to the descending portion of the duodenum—the hepatocolic ligament. This ligament, however, is not constantly present. From the above description it is evident that the hepatoduodenal and hepatocolic ligaments play an important rôle in the fixation of the superior segment of the duodenum. These ligaments are responsible for the maintenance of the looping of the redundant duodenum.

In this study I desire especially to call attention to a redundant condition of the superior portion of the duodenum. This is an interesting anomaly which frequently passes unrecognized. During our routine roentgenologic study of the gastrointestinal tract I have encountered in a number of instances an elongation or lengthening of the superior portion of the duodenum. In all, a ptosis of this segment resulting in an abnormal loop was observed, which produced a puddling and retardation of the contrast meal like a water trap in which the passage of the opaque meal is somewhat blocked. The superior angle appears definitely fixed and displaced distally. In addition, the superior segment of the duodenum is fixed at its proximal portion, viz., at the junction of the first part or cap with the second part of the duodenum. The unusual lengthening of the superior segment results in a sagging, ptosis and looping, producing the characteristic picture of the redundant duodenum. The two fixed points in the superior portion are well illustrated in Figs. 1, 2 and 3.

Roentgenologically this elongated segment of the superior duodenum varies in length from 5 to 10 cm. Several types have been observed, such as the U-shaped, V-shaped, double looping and the serpentine forms. Occasionally only a sagging of the elongated segment is noted. These types are illustrated in Fig. 1.

Under normal conditions the Roentgen examination of the duodenum presents the first portion or bulb surmounted directly upon the pyloric outlet, which is directed upward, slightly to the right and somewhat posteriorly. This is commonly known as the superior

portion and is usually not more than 5 cm. in length. At the apex of the bulb or duodenal cap, the second portion is observed to form an angle with the first part and then descends downward to the right and posteriorly. No transverse elongation of this section of the duodenum is observed normally. The angulation of the superior portion is easily recognized and is more or less fixed by the hepato-duodenal ligament. From this angulation the descending portion seems to take a sudden drop. However, where the redundant duodenum is noted, this picture is quite altered into a marked elongation or lengthening of the superior segment. The duodenal cap is not

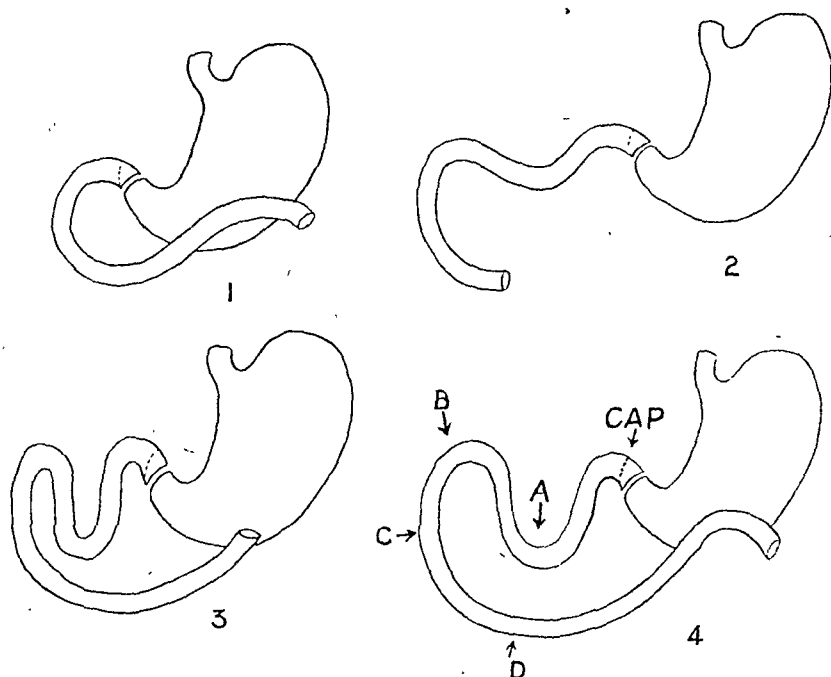


FIG. 1.—Diagrammatic drawing, illustrating the redundant duodenum. 1. Normal duodenum; 2, sagging elongated superior segment; 3, V-shaped, water trap effect of superior duodenum; 4, U-shaped, A, B, C, D, described in Fig. 2.

affected and seems to be normal in position and in size. In some instances at first glance the extra loop appears as an integral part of the cap which produces the appearance of an enlarged cap or diverticulum. This is due to the coalescing of the extra loop with the cap shadow, but upon manipulation no connection with it can be demonstrated.

Redundancy of the Superior Duodenum and its Clinical Significance. This form of anomaly has been variously described as ptosis, festooning or extra looping, terms which cannot be considered satisfactory. It is apparent that, since the duodenum is of greater

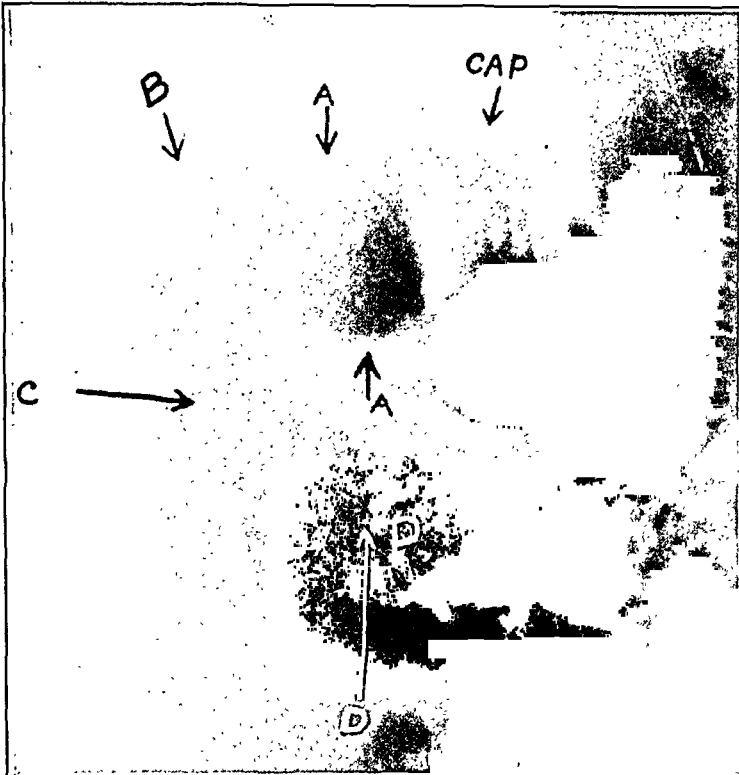


FIG. 2

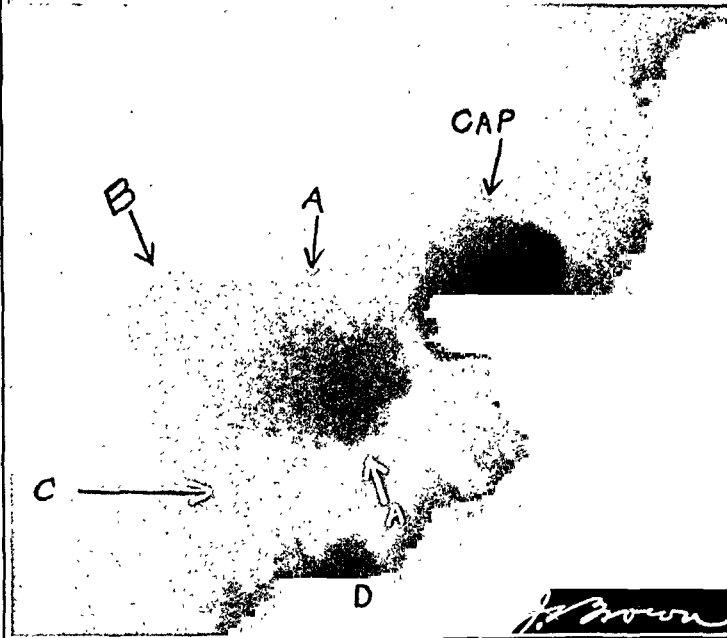


FIG. 3

FIG. 2.—The lengthened duodenum with looping at A. This also illustrates the two fixed points. 1, at cap, representing the hepatoduodenal fixation, and 2, at B, the hepatocolic fixation; C, descending duodenum; D, transverse portion.

FIG. 3.—The unusual length of the superior duodenum with the extra loop, or water trap at A is shown.



length than normal, the term redundant duodenum should be adopted as being more accurate as well as descriptive, and fitting more definitely with such redundant affections of a similar type as, for example, the redundant colon.

The material selected for this study comprises a group of 10 cases, all of which present a definite elongation of the superior portion of the duodenum with sagging and looping of the segment. Increasing interest is now being attached to this anomaly due to its effect upon the motility of the duodenum and the production of a condition which may have considerable significance in the formation of ulcerations in this area. As a result of the diminished motility with consequent stasis as well as retardation and lagging as is revealed by the contrast meal, this factor may easily play an important rôle in the production of such disturbances. An early recognition of this anomaly is essential in order to establish effective treatment, which should be instituted early so as to eliminate the possibility of secondary complications which may readily occur. In the diagnosis, other factors simulating this anomaly must be borne in mind, such as adhesions of the duodenum secondary to a gall bladder infection.

The redundant duodenum must be regarded as a definite easily recognized roentgenologic entity. These cases rarely present any signs of gall bladder infection. On the other hand, in nearly every instance in this series a typical or atypical picture of an ulcerated duodenum was found. In some instances, even when the roentgenologic appearance of ulceration is absent, the clinical picture frequently is that of ulcer. The association of ulceration with this anomaly is very significant. In those instances in which ulceration was not found, Roentgen evidence of duodenitis was observed.

In this series of cases the Roentgen examination presented evidences of ulceration in 5 instances; duodenal in 3, pyloric in 1 and gastric in 1. Duodenitis was present in the remaining 5 cases. Duodenal stasis, lagging and retardation was observed in every instance.

It seemed of importance to determine whether the relative position of the stomach and colon had any definite relationship to that of the redundant duodenum. In 5 instances the position of the stomach and colon was observed to be normal; in 1 a slight ptosis was noted; in 1 a moderate ptosis and in but 3 was there marked ptosis of the stomach and colon. It may, therefore, be concluded, at least from these findings, that the position of the stomach and colon bears no special relationship to the redundancy of the duodenum.

The gastric acidity was normal in 3 cases; a hyperacidity occurred in 6 and an achylia in 1.

Age seems to be an unimportant factor. In this series the ages ranged between 26 and 57 years.

Sex. There were 8 males and but 2 females in our cases, indicating that the redundant duodenum is probably more frequent in the male sex.

The diagnosis is not, as a rule, possible from the history and physical findings and must be based largely upon a Roentgen investigation. Though the condition is best recognized under the fluoroscope, this anomaly may also be recorded on the films, when placed in the proper position. The fluoroscopic examination is usually best made with the patient in the upright posture, viewed anteroposteriorly, obliquely and laterally. Examinations should also be made routinely in the prone position. In the fluoroscopic examination one can manipulate the entire duodenum and especially bring into view the redundant segment, which may otherwise not be visible. Most frequently one observes a puddling in a loop hanging from the midsuperior portion of the duodenum, between the cap and the descending sections. As has already been stated this has the appearance of a water trap, which definitely retards the outflow of the contrast meal and which at once gives a clue as to the possibility of the presence of this abnormality. On manipulation this puddling entirely disappears, only to return on the next spurt of the opaque meal through the duodenum.

Roentgenologically a double fixation of the superior duodenum is presented in this group of cases, which is not due to acquired adhesions, but represents most likely a congenital anomaly. The fixation is due to the presence of peritoneal bands, represented by the hepatoduodenal and the hepatocolic ligaments. The presence of a redundant superior duodenum is best explained upon the basis of a congenital formation, in which the duodenum is lengthened, so that it cannot fit into the space allotted to it. This anomaly therefore seems to be dependent upon the unusual length and abnormal fixation of the superior portion of the duodenum.

As a result of this anomaly, the duodenum frequently becomes irritable and produces the Roentgen signs of a duodenitis. A prolonged stasis was not observed in our cases. The caliber of the duodenum was not enlarged nor was there any evidence of chronic obstruction. No abnormal or exaggerated retroperistalsis was observed in this group.

Conclusions. 1. Ten examples of redundant duodenum have been studied and their significance evaluated.

2. The redundant segment occurs most frequently in the superior portion.

3. The redundant duodenum is not an infrequent condition, being more common than is ordinarily recognized.

4. The clinical significance of the redundant duodenum has as yet not been fully established.

5. The coexistence of ulceration with the redundant duodenum is not unusual.

6. The Roentgenologic method of examination offers the best possible means of establishing the diagnosis.

**THE CORRELATION OF OTHER DIAGNOSTIC PROCEDURES
WITH CHOLECYSTOGRAPHY IN 250 CASES OF
SUSPECTED GALL BLADDER DISEASE.**

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THE following analysis of data on 250 recent ambulant and hospitalized patients who, on cholecystographic study, gave evidence of gall bladder disease has been made with two purposes in mind: to test further the reliability of that diagnostic procedure and to determine to what extent other common factors in diagnosis could be correlated with it. No selection of cases has been made except to omit such suspected ones as had negative cholecystograms. This both eliminates the possibility of detecting cholecystographic errors in which disease is present, but is not demonstrable roentgenologically, and fails to give convincing proof of the presence of disease in the cases not operated upon. With these limitations, however, it seems a reasonable approach to the matter of evaluating the significance of the roentgenologic diagnosis of gall bladder disease. At the same time it affords an opportunity to place a relative value on all the diagnostic procedures commonly employed.

The two propositions just outlined were checked by operation in 74 instances (30 per cent). In 176 cases each diagnostic procedure was evaluated in the light of the conclusion reached from the assembled clinical data of the case.

The clinical history, physical examination and cholecystogram now comprise in most clinics an irreducible minimum in the diagnostic study of gall bladder disease not associated with common duct obstruction. In addition to these procedures, which were carried out on all patients of the present series, the following tests were performed in sufficient number to be of statistical value: fractional gastric analysis after a gruel test meal in 184 patients, after histamin in 8, gastrointestinal roentgenography in 117, van den Bergh test in 108 and duodenal drainage by the technique of Jones¹ in 95. An attempt is made to determine the significance in diagnosis of the incidence of other disease along with cholecystitis. Follow-up data on the surgically treated cases are included for the sake of completeness.

The position of the Graham-Cole test as a diagnostic aid is being constantly strengthened by perfection of the technique and by the

publication of comparative figures such as these. In a former paper² the limitations of both peroral and intravenous cholecystography as practised in this hospital were summarized and the conclusion reached that in doubtful cases the intravenous method should be used as a check on the routine peroral test.

Recent reports on the effectiveness of special diagnostic tests include cholecystography, but fail to correlate with it all the other commonly used procedures. Bockus³ expresses the position of those who depend upon duodenal drainage rather than cholecystography for the diagnosis of gall stones. Kirklin,⁴ with a wide experience in cholecystography and a progressive attitude toward it, represents those whose reliance is placed very largely in that procedure. Dwyer and Dowling⁵ present diagnostic data in regard to history, cholecystography and gastric analysis, in a report dealing particularly with the effects of cholecystectomy. Hoffman⁶ studied 155 surgically treated cases to determine the degree of accuracy of certain diagnostic procedures, with emphasis, however, on the clinical data. Fleming,⁷ in an appraisal of his experience in 233 proved cases, analyzed the diagnostic reliability of the Graham-Cole test alone.

Clinical History. The emphasis to be placed in this review upon cholecystography and other laboratory tests is by no means meant to detract from the value of a well-taken history. The history will be considered first because it emerges, upon analysis of these cases, the most effective single diagnostic item in 126, or half of the series. It remains the chief support in most cases for the clinician's judgment, as Hoffman⁶ has recently emphasized. The consistency with which the major symptoms of intermittent right upper abdominal pain and persistent "gaseous indigestion" occur is noteworthy: One or both were present in almost every case. Other items of the history, less frequently found, will be recapitulated because their value was proved in these cases: Familial history of gall tract disease, preceding pregnancies in the patient, adiposity, distress after fatty or "rich" foods, sudden onset of pain, night attacks, nausea and vomiting, necessity for hypodermics and residual local soreness.

In general, we have not attempted to distinguish between gall stones and mere diseased gall bladder wall from the history and physical findings in the absence of jaundice. The contention that distress or pain after eating fatty foods is a differentiating symptom of cholecystitis with stones was not confirmed. In the 64 operatively proved cases distress after fatty food had occurred as a symptom in almost the same proportion of those patients who did not harbor gall stones as those who did, a distinct minority in each class. (Present in 14 cases with stones, absent in 34; present in 4 cases without stones, absent in 12.)

The age incidence of this group of patients is in accord with the

figures commonly accepted. About 80 per cent began to have symptoms between the ages of 20 and 50 years, and the same proportion presented themselves for treatment when they were between 30 and 60 years. Dwyer's figures⁵ of 35 per cent below the age of 40 years at admission are duplicated (36 per cent).

TABLE 1.—SEX AND AGE INCIDENCE ON ADMISSION IN 250 CASES OF PROVED OR SUSPECTED GALL BLADDER DISEASE WITH POSITIVE CHOLECYSTOGRAMS.

Sex.	Number.	Per cent.
Females	169	68.0
Males	81	32.0
Decade		
10 to 19	2	0.8
20 to 29	24	9.7
30 to 39	63	25.0
40 to 49	78	31.2
50 to 59	50	20.0
60 to 69	31	12.5
70 to 79	2	0.8
	250	100.0

TABLE 2.—AGE INCIDENCE IN 235 CASES AT TIME OF ONSET OF SYMPTOMS.

Decade.	Number.	Per cent.
10 to 19	4	1.7
20 to 29	48	20.2
30 to 39	70	30.2
40 to 49	67	28.5
50 to 59	30	12.5
60 to 69	15	6.5
70 to 79	1	0.4
	235	100.0
Uncertain of time of onset	15	

The above age incidence figures offer nothing helpful in the differential diagnosis from peptic ulcer, a point which merits reiteration. The age curves both at onset and at admission can almost be superimposed upon those for 221 cases of proved duodenal ulcer reported in 1929 by Miller, Pendergrass and Andrews.⁸ The age-at-onset curve likewise approaches closely that of Taylor and Miller⁹ for a group of patients with gastric cancer believed to have arisen on an ulcer basis. (Charts I and II.)

The sex incidence figures, however, vary widely for the two groups. In the gall bladder series women predominated 2 to 1; in the ulcer series men outnumbered women 6 to 1. Unfortunately, no anthropometric data as worked out by George Draper are available.

Physical Examination. Tenderness in the gall bladder area was present in 70 per cent. The liver was palpated in 19 per cent, the gall bladder itself in only 8 instances (3 per cent). A definite Riedel lobe was described only 3 times in 250 examinations. Muscle resistance was infrequently mentioned, and presumably infrequently determined. There is likewise no indication on the records as to

the extent to which the tests for intercostal neuralgia (Carnett) were applied. Nine per cent of the group showed clinical jaundice at the admission examination.

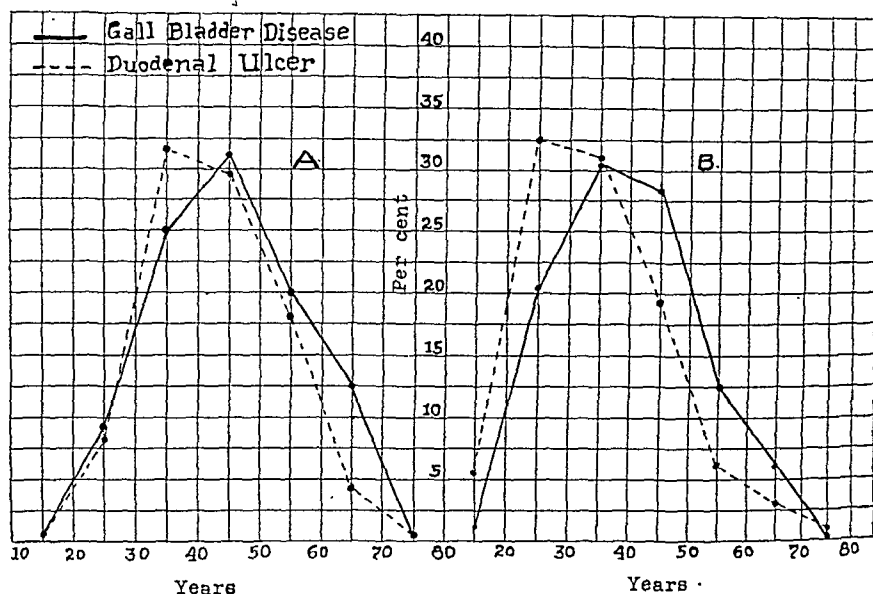


CHART I.—A, age incidence at time of admission to hospital of 250 gall bladder and 221 duodenal ulcer cases. B, age at onset of symptoms in 235 gall bladder and 221 duodenal ulcer cases.

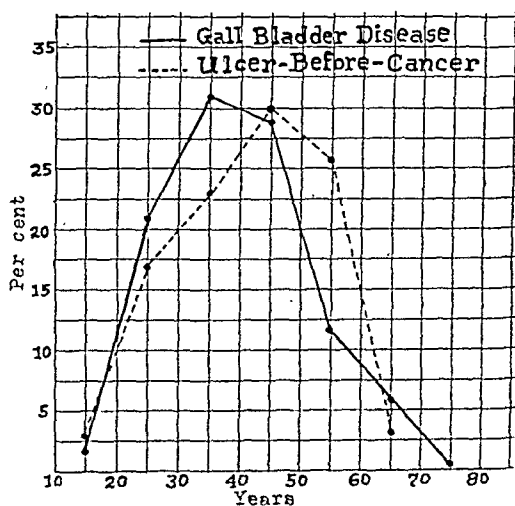


CHART II.—Age at onset of symptoms in 235 gall bladder and 31 gastric ulcer-before-cancer cases.

In summary, the records reveal a tendency to slight the secondary physical signs in these patients, and partly as a result of this the examination outvalued the history and cholecystogram as a factor in diagnosis only 9 times.

TABLE 3.—SYMPTOMS AND SIGNS.

	Number.	Per cent.
Upper abdominal pain	214	86.0
Indigestion	177	71.0
Jaundice (history)	50	20.0
Tenderness in gall bladder area	171	69.0
Liver palpable	48	19.0
Gall bladder palpable	8	3.2
Jaundice (observed)	31	12.4

Cholecystography. The Graham-Cole test compared most favorably with the history as a trustworthy diagnostic guide. It was found, after all clinical facts were in hand, to be the most valuable diagnostic item in 115 cases (compared to 126 in which the history outvalued it). The test was performed on all patients: 248 patients took the dye by mouth; 56 intravenously, in general as a check on the peroral method.

TABLE 4.—CHOLECYSTOGRAPHY VERSUS CLINICAL HISTORY AND PHYSICAL EXAMINATION.

	Number.	Per cent.
Oral cholecystograms	248	99
Intravenous cholecystograms	56	22
History most valuable item	126	51
Cholecystogram most valuable item	115	46
Physical findings most valuable item	9	3

Here, as elsewhere, one notices an occasional overstressing of the positive cholecystogram, and tendency to slight the history and other factors in diagnosis. Kirklin⁴ and others have stated that the most common source of error in cholecystography is the "normally functioning gall bladder" which nevertheless reveals calculi and inflamed walls to the surgeon. On the other hand, 10 of the 74 cases of this series subjected to operative proof demonstrate again that the roentgenogram of a "poorly functioning gall bladder" occasionally is due to other than gall bladder disease or, indeed, to no adequate cause. These 10 individuals were regarded at operation as having normal gall bladders which were left *in situ*. Their cholecystograms had been made by the peroral technique and were carefully reviewed: All showed the homogeneous opaque substance in the intestinal canal which indicates that absorption of the dye has occurred. In 8 a plausible reason for the absence of shadow lay in abnormality of organs closely associated with the biliary tract (*i. e.*, liver disease, duodenal ulcer, cancer of the pancreas and pyloric stenosis). In this connection Rivers¹⁰ has

stressed the propinquity of duodenum and gall bladder, whereby an inflammatory condition in one organ may alter the function of the other or extend to and involve it to a varying degree. Two of the 8 cases were jaundiced at the time of cholecystography and the error may have been due to this.

In 2 instances, however, operation disclosed a grossly normal biliary system and no disease of adjacent organs. In both the appendix was involved (subsiding acute appendicitis and adherent retrocecal appendix), which may have influenced the cholecystogram in a manner obscure at present. One, therefore, cannot in justice determine the true cholecystographic error in this rather large proportion of disagreement in findings. Furthermore, pathologic examination of the mucosa and walls of these gall bladders might have disclosed disease not evident to the surgeon but sufficient to interfere with function. The above 10 cases are included in the series because, largely due to the cholecystogram, they fell into the group "suspected gall bladder disease," although the pre-operative diagnosis may have been that of other abdominal disorders. They illustrate the danger of the error that lies in over-much dependence on a single test, no matter how efficient.

TABLE 5.—OPERATIVE FINDINGS IN THE 74 OF 250 CASES WITH POSITIVE CHOLECYSTOGRAMS THAT CAME TO LAPAROTOMY.

Gall bladder disease	64
Gall bladder normal, other abdominal lesions	10
Cirrhosis of liver	2
Duodenal ulcer	2
Carcinoma of pancreas with jaundice	1
Pyloric stenosis	1
Narrow common duct, with pyloric stenosis	1
Spastic duodenum, excess motility	1
Appendicitis	2

Gastrointestinal Roentgenography. We have made roentgenologic study of the stomach and intestine with the opaque meal in 47 per cent of the present series. Although detailed studies of the relationship of the alimentary tract to the abnormal gall bladder were not made, it is significant that the duodenum was deformed by adhesions in 53 per cent of the 117 cases. Among 30 proved cases 60 per cent showed such duodenal deformity. Duodenal stasis occurred in 10 per cent, while in only 24 per cent of the total was the upper gastrointestinal tract normal roentgenologically.

The procedure is indicated in obscure cases, in our opinion. The helpful diagnostic evidence to be obtained from such study is seemingly not appreciated in many American clinics, so that Rossi of the University of Parma, in describing the valuable features of his combined cholecystographic and gastrointestinal technique," can with some justice write: "Almost always, especially abroad, there has been omitted an accurate study of the gastrointestinal tract." He gives the patient an opaque, fatty paste instead of the

fatty meal, and studies serially the shape, position and functional activity of the stomach and intestine while the gall bladder is contracting. Levene and Whitaker,¹² in 1930, reported good results from the simultaneous observation of stomach, duodenum and gall bladder action. Nevertheless, possibly due to the rather exacting and time-consuming technique, the combined method has not gained wide acceptance in this country.

TABLE 6.—GASTROINTESTINAL ROENTGENOGRAPHIC FINDINGS.

	In 117 patients with positive cholecystograms.		In 30 cases of diseased gall bladder at operation.	
	Number.	Per cent.	Number.	Per cent.
Deformed duodenum (adhesions)	62	53	18	60
Normal	29	24	5	17
Upper intestinal stasis	11	10	2	7
Pylorospasm or deformed pylorus	7	6	3	10
Duodenal ulcer	6	5		
Gastric polyp	1	1	1	3
Excess motility	1	1	1	3

Duodenal Drainage. This procedure has been in use in our Gastrointestinal Section since 1927. The early results on a small group of patients were reported in 1929.¹³ Throughout, the technique advocated by Jones¹ has been followed with the following results in 95 cases (31 per cent): Half of the examinations offered confirmatory evidence of cholecystic disease; the other half gave results which were not helpful, in that the findings in the centrifuged sediment were entirely negative, when other evidence pointed to disease, or when in the absence of definite crystals the examiner could not be certain that the formed elements seen denoted true biliary pathology. Approximately the same results appeared in 30 cases subsequently proved.

TABLE 7.—DUODENAL DRAINAGE IN 95 GALL BLADDER SUSPECTS.

	Number.	Per cent.
Of diagnostic value (Crystals, 33)	46	48
Doubtful value (Negative, pus cells, epithelium)	25	26
No value (Disagrees with final diagnosis or operative findings)	24	26

TABLE 8.—DUODENAL DRAINAGE IN 30 CASES OF PROVED BILIARY DISEASE.

	Number.	Per cent.
Crystals	12 {stones, 10}	41
Excess pus cells	5 {gall bladder ulcerating, 2 stones, 2}	16
Negative	10 {no stones, 6 stones, 4}	33
Doubtful	2	6
Unsatisfactory	1	3

The negative drainages in positive cases, which have formed the bulk of the unsatisfactory tests to date, have, in our present

more complete knowledge of the method, been due in large part to two factors: The impossibility, until recently, in the Section or the wards of assigning the conduct of the test to a single thoroughly trained member of the staff, and an insufficient number of diagnostic drainages in the doubtful cases. Those who have reported great success with the test³ emphasize these points. Our results have demonstrated that to be of consistent value, every step of the technique must be presided over by an expert. Provided the conditions are fulfilled, there is no doubt that the failure to obtain brown gall bladder bile or the finding of cholesterol or calcium bilirubin crystals or large numbers of deeply bile-stained pus or columnar cells is evidence of gall bladder disease.

Gastric Acidity. Analyses of the gastric contents were made with the gruel test meal in 184 of the entire group and 53 of the proved cases. The histamin test was made 31 times, in 23 instances after the gruel meal had developed little or no free acid. Of the 23 patients, 17 showed adequate acid figures under the increased stimulus. However, because of the great variability of response to histamin, precluding any "normal" standard, and because the histamin series is quite small, it is not deemed worthwhile to include it in the tabulation. Histamin is used at present in the Section only to distinguish true from false achlorhydria.

The results of the gruel meal are likewise hard to standardize and comparison with the figures in other published reports is almost worthless because of the great variation that prevails in the type of meal used and the technique of collection. However, setting the limits of 10 to 40 (cc. $\frac{N}{10}$ HCl per 100 cc.) for normal range of free acid response in the 90-minute fractional test, with gruel, the incidence of hypochlorhydria and achlorhydria in the general and the proven groups was 38 and 31 per cent, respectively. This is a distinctly higher proportion than obtains for the patients of the Section as a whole. The patients showing excess acid secretion were in small number, 10 and 4 per cent, respectively.

TABLE 9.—GASTRIC CONTENTS (FRACTIONAL ANALYSIS, GRUEL MEAL).

	In 184 patients with positive cholecystograms.		In 53 operatively proved cases.	
	Number.	Per cent.	Number.	Per cent.
Normal	96	52	34	65
Hypochlorhydria	43	23	7	12
Achlorhydria	28	15	9	19
Hyperchlorhydria	17	10	3	4

With 2 exceptions to be mentioned, the hyperchlorhydria patients gave the histories of short duration and the patients with depressed acid as a rule the longer ones. The average duration of symptoms in the high acid group including 1 12- and 1 15-year history was 3.6 years. The average for the same hyperchlorhydria patients, with these 2 histories omitted, was 2.4 years. In comparison, the

average duration for the low acid cases was 4 years; and for the normal acid cases 3.1 years.

One is justified, probably, from these results, in saying that evidence is hereby added that hypochlorhydria and achlorhydria are more common in gall bladder disease than in normal persons and gastrointestinal patients other than those with gastritis or malignancy. Furthermore, the incidence of hyperacidity is relatively small, and the condition is found, by and large, early in the disease. The discovery of depressed or absent free hydrochloric acid may thus be of use, with an extended history of indigestion, as a link in the chain of diagnostic facts denoting gall bladder pathology.

Van den Bergh Test. In the presence of clinical jaundice the van den Bergh test, repeated every few days, is of value in determining whether any regression of the jaundice is occurring. Its chief value, however, lies in the ability of the indirect reaction, with the icterus index, to pick up latent jaundice, not detectable otherwise. In the doubtful case such indication of liver or biliary tract abnormality may clinch the diagnosis. The test was performed 1 or more times on 108 individuals. It demonstrated latent jaundice, not detectable clinically, in 22 per cent; among the proved cases in 29 per cent. The test is worthy of retention in gall bladder diagnosis, indeed of more frequent application than was made in the present series.

TABLE 10.—VAN DEN BERGH TEST.

	In 108 patients with positive cholecystograms.		In 24 operatively proved cases.	
	Number.	Per cent.	Number.	Per cent.
Negative	56	52	9	38
Direct positive (jaundice)	29	27	8	33
Indirect alone positive (latent jaundice)	23	21	7	29

TABLE 11.—VERIFIED COMPLICATING LESIONS IN 250 CASES.

Heart disease:		Duodenitis	1
Myocardial (with symptoms)	13	Carcinoma, primary, in duo-	
Chronic valvular	2	denal wall	1
Appendicitis:		Gastric polyp	1
Acute	1	Diabetes mellitus	4
Chronic	6	Hypertension	4
Liver disease:		Syphilis	2
Hepatitis	6	Renal calculus	1
Catarrhal cholangitis	2	Pyelonephritis	1
Carcinoma (primary)	1	Toxic goiter	1
Duodenum:		Colitis	1
Ulcer	3		
Diverticulum	1		52

Complicating Diseases. This group of cases is too small to offer evidence of value in determining the diseases most likely to be associated with cholecystitis. It does, however, bear out the impression widely held, and recently put in tabular form by Rivers and Hartman,¹⁰ of the high proportion of coincident disease. The

proved coexisting lesions among these 250 individuals were divided among 13 disease groups, and occurred in more than one-fifth of the cases (21 per cent). Myocardial disease with symptoms was perhaps more frequent here (5 per cent) than among the population at large of similar age range.

Follow-up. The figures of the results of surgical treatment, included by courtesy of Drs. Müller and Eliason, on whose services the patients underwent operation, are included simply to indicate the type of result to be expected from conservative surgery in contrast to the known poor result of any medical therapy.

TABLE 12.—FOLLOW-UP, 4 MONTHS TO 3 YEARS, ON 50 PATIENTS WITH OPERATIVELY PROVED GALL BLADDER DISEASE.

	Well.	Improved.	Unimproved.	Died.
Cholecystectomies, 43.				
Cholecystitis	3	1	1	2
Stones in gall bladder	21	7	2	0
Stones in common duct	2	0	2	2
	<hr/>	<hr/>	<hr/>	<hr/>
Totals	26	8	5	4
Cholecystostomies, 7.				
Cholecystitis	0	2	0	0
Stones in gall bladder	3	2	0	0
	<hr/>	<hr/>	<hr/>	<hr/>
Totals	3	4	0	0

Conclusions. 1. The diagnostic procedures in gall bladder disease which have proved of most value in this clinic are, in order of their effectiveness in 250 instances: (1) A careful and complete history and physical examination; (2) cholecystogram; (3) gastrointestinal roentgenography; (4) duodenal drainage; (5) the van den Bergh test and icterus index; (6) fractional gastric analysis.

2. Gastrointestinal roentgenography can be made of more positive value in diagnosis of cholecystic disease than is the case at present.

3. Duodenal drainage can be made effective in diagnosis by very careful routine technique and examinations to be made only by a thoroughly trained person, preferably a physician. Otherwise the procedure is not worth the time and effort involved.

4. While each one of these procedures will not be needed in every instance of suspected biliary disease, together, if carefully done, they are adequate to give in the doubtful case sufficient data to warrant decision for or against laparotomy.

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THE PERSONALITY TYPE OF PATIENTS WITH ARTERIOLAR ESSENTIAL HYPERTENSION.

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It has long been believed that patients with arteriolar essential hypertension have special physical and emotional reactions to life—in other words, that such patients have a special type of personality. If this is true, then the knowledge and application of this fact may not only aid the diagnosis and therapy of this disease, but may afford insight into its etiology. Unfortunately, the evidence for this idea of a special hypertensive type consists almost wholly of clinical impressions. It has been the purpose of the present investigation to test the validity of these clinical impressions by controlled study.

Literature. In accord with many writers on this aspect of the subject, Mosenthal¹ states that arteriolar (essential) hypertension "occurs rather more frequently in the highstrung, nervous, or irritable individual." Likewise O'Hare² says that "almost all have been of a nervous temperament throughout life." Herrick³ believes that hypertensive patients have an "ill-balanced personality" whose chief tendencies are "pressure of activity and over-earnestness." He says further that they are "serious, earnest, conscientious, enthusiastic at work, at their infrequent play, and too often at table." Barach⁴ finds that early in life hypertensive patients have "a certain instability, restlessness, a lack of confidence and shirking of responsibility . . . During middle life . . . they frequently are restless or ineffectual, or they may be abnormally active and intensive in their special field of endeavor." Moschcowitz⁵ has presented one of the most detailed and interesting descriptions of the hypertensive type. He has observed among other things that "the greatest proportion of patients with hypertension are terribly tense and pursue their vocation with tremendous seriousness, and

worry over trivialities. In consequence, they are irritable. They are the antithesis of the child. They do not play. They have no time for play. They have narrow intellectual horizons." In general, the above writers believe that hypertensive patients tend to be highstrung, serious, and overactive.

Several physicians have tried to verify these valuable clinical impressions by more exact studies. O'Hare, Walker and Vickers⁶ analyzed the records of 300 hypertensive patients whose average age was 51 years. They found that 42 per cent had one or more of the following symptoms in their early history: "Frequent epistaxis; abnormal flowing at menstruation; migraine; cold, sweaty, and cyanotic hands; flushing; blushing; extreme sensitiveness; a highstrung and nervous temperament, etc. In 100 of these hypertensive patients, who were questioned especially for these symptoms, we were able to establish their presence in 87 per cent." By contrast, in 436 patients with normal blood pressures whose average age was 36 years, these "symptoms of vasomotor weakness, etc., were noted in only 23 per cent" of the records analyzed. On the other hand, the studies of Patek and Weiss⁷ showed no striking differences in personality between a group of 47 hypertensive patients and 37 patients with normal blood pressure. On questioning their patients they found that 67 per cent of the hypertensive patients were "excitable" as compared with 54 per cent of the control group; 75 per cent of the hypertensive patients were "hyperactive" as compared with 65 per cent of the control group; 53 per cent of the hypertensive patients were "impulsive" as compared with 37 per cent of the control group; and 83 per cent of the hypertensive patients "worried excessively" as compared with 54 per cent of the control group. Thus, the only definite "difference between the two groups was in their relative propensities to worry."

Neither of these studies offers adequate proof for or against the existence of a special hypertensive personality. O'Hare, Walker and Vickers studied the psychic and vasomotor reactions of only the early life of hypertensive patients, without inquiring into the reactions of these patients during their later years. Furthermore, the average age of the control group was 15 years less than the average age of the hypertensive group so that many in this younger control group might develop hypertension in the following 15 years. In the study of Patek and Weiss, no mention is made of the age of their patients other than that both groups had "similar age distribution." Most important, they do not state the method of questioning their patients or the questions asked. This information is essential in evaluating their results. It is easy to obtain affirmative answers from the majority of people who are asked, for example, "Are you sensitive?"; a much smaller number will respond in the affirmative to the question "Are you unusually sensitive?"; while a still smaller number will give positive answers to the question, "In

general, have you been more sensitive than the average person?" In neither of the above studies was mention made as to what was considered normal blood pressure. Both of the studies were carried out on ward patients and, therefore, many of the normal patients may easily have had mild hypertension which dropped to normal during bed rest or during inactive ward life.⁸ Furthermore, in both of the studies, the control cases were sick ward patients. Therefore, these control patients were not healthy normal people, but sick patients with normal blood pressure. The above studies really constitute a comparison of the personality type of hypertensive patients with the personality types of patients with peptic ulcer, bronchial asthma, tuberculosis, carcinoma, etc., who had normal blood pressure. Diseases like peptic ulcer, for example, may possibly occur in people of certain personality types,⁹ so that the personalities in the control groups of the above studies are not those of a truly normal group of people. The literature, therefore, indicates the need of further study of the personality in hypertensive patients.

Clinical Material of Present Study. The clinical material used in the present study consisted of 182 ambulatory "patients" seen in dispensary and private practice. The details of age, sex, weight, blood pressure, etc., of these patients are presented in Table 1. The standards of normal blood pressure used in this study are those of Rogers and Hunter.¹¹ The subjects fall into the following 5 clinical groups:

TABLE 1.—CLINICAL MATERIAL OF PRESENT STUDY.

Groups.	Number of patients.	Number of females.	Average age of group, yrs.	Range in age.	Range of systolic blood pressure, mm. of Hg.	Range of diastolic blood pressure, mm. of Hg.	Average weight of group above normal standard for age and height, in pounds.*
1 . .	41	28	54	36 to 74	160 to 280	90 to 160	14.7
1a . .	20	11	56	39 to 67	160 to 260	92 to 158	7.0
2 . .	34	12	26	15 to 35	150 or more in 50% 140 or more in 80%	90 or more in 33%	11.3
3 . .	35	12	47	36 to 71	130 or less in 75% 130 to 140 in 25%	less than 90 in 86% 90 to 100 in 14%	8.0
4 . .	52	17	25	15 to 35	130 or less in all 124 or less in 70%	80 or less in all 70 or less in 50%	5.5

* See No. 10 in bibliography.

Group 1. Middle-aged hypertensive patients with symptoms.

Group 1a. Middle-aged, symptom-free, hypertensive patients. Most of the patients in Groups 1 and 1a had secondary cardiac enlargement and retinal vascular changes, while a few had mild secondary renal damage.

Group 2. Young hypertensive individuals. Twenty-one of the patients in this group made two or more visits, and 50 per cent of those seen on a second visit still had abnormally high systolic pressures. Only 2 patients continued to have abnormally high diastolic blood pressures at the second visit. Twenty-five of the subjects in Group 2 were children of parents with definite essential hypertension, were symptomless, and had not requested medical attention. The parents had been examined by the author.

Group 3. Middle-aged control subjects with normal blood pressure. Most of the patients in this group were either healthy people who wished a general examination, or ambulatory people referred for general medical examinations because of uncomplicated gonorrhea, obesity, skin diseases, primary syphilis or varicose veins. All of these patients had few if any symptoms.

Group 4. Young control subjects with normal blood pressure. Twenty-seven of the 52 patients were referred for general medical examinations because of uncomplicated gonorrhea or skin diseases. They had few, if any, symptoms. The remaining 25 subjects were children of parents with definite essential hypertension, were symptomless, and had not requested medical attention. Their parents had been examined by the author.

Method of Present Study. The same specifically worded direct questions in regard to personality were asked of the control subjects and the patients with hypertension. There was no hesitancy by the author of employing direct questions because both control and hypertensive subjects were subjected to the same method of questioning. This method of allowing the subject to evaluate his own personality is considered very satisfactory when dealing with nonpsychotic individuals who have no reason to conceal anything. Only subjects who readily grasped the questions were utilized. It was a striking fact that the great majority of people were able to give a prompt reply to the questions asked. It might be argued that hypertensive patients may possibly be more introspective than subjects with normal blood pressure. This possible error was found to be absent, for, on inquiring in many cases among the intimate relatives of the subjects, the relatives agreed that the subjects evaluated their personality quite accurately. Each subject was questioned in such a way as to avoid as far as possible being influenced by the tone of the questioner. In about 20 per cent of the subjects the personality study was made before the blood pressure reading was determined. The questions selected referred partly to personality characteristics commonly mentioned in the literature as associated with hypertension, and partly to personality traits with which I personally have been impressed in hypertensive patients.¹² The entire study, including determinations of the blood pressure, was carried out by the author. The blood pressure was determined by the mercury sphygmomanometer and auscultation. The end of the third phase was the criterion of diastolic blood pressure. The complete list of the questions as they were asked is as follows:

1. In general, throughout your life, not on any one special occasion, and compared to the average person of your own age with whom you have come in contact, have you been of an unusually highstrung nature or of a calm nature?

2. In general, throughout your life, not on any one special occasion, and compared to the average person of your own age with whom you have come in contact, have you been the sort of person who loses his temper quickly (who flies off the handle easily over little things) or has it usually required a good deal to make you lose your temper?

3. In general, throughout your life, not on any one special occasion, etc. . . . (as in Question 2) . . . have you been the sort of person who even if you don't show it externally, feel yourself frequently getting all excited over little things?

4. In general, etc. . . . (as in above questions) . . . have you been the sort of person whose feelings are unusually easily hurt, who is unusually sensitive, or does it take a great deal to make you feel hurt?

5. As a younger person did you or do you still blush or flush unusually easily compared to the average person your age? Would people "kid you about it?"

6. As a younger person, did you or do you still become unusually easily embarrassed compared to the average person?

7. In general, etc. . . . have you been the sort of person who worries unusually easily over little things, or have you tended to pass them over?

8. In general, etc. . . . (as in Questions 1 and 2) . . . have you been of an unusually serious nature or of a happy-go-lucky nature?

9. In general, etc. . . . have you been of an unusually forward or unusually shy nature?

10. In general, etc. . . . have you ever had frequent nosebleeds?

11. In general, etc. . . . have your hands or feet tended to become easily cold on slight changes in weather?

12. In general, etc. . . . have you tended to walk at an average pace, slower than the average person, or faster than the average person?

13. In general, etc. . . . have you tended to work at an average pace, slower than the average person, or definitely faster than the average person?

14. In general, etc. . . . have you tended to eat or talk at an average rate, slower than the average person with whom you eat (or talk) or faster than the average person.

15. In general, etc. . . . have you been of average, less than average, or more than average physical activity?

Only definite replies were used, so that when a patient stated that he could not definitely answer, that particular patient was not credited with any reply to that special question. Where the patient stated that a particular trait had existed in him for only a few years rather than his whole life, he was credited as not having that trait throughout his life, that is, from the point of view of the present study, that trait was absent most of his life.

Results. The results of the questioning are presented in Tables 2 and 3. Let us temporarily omit a consideration of the selected Group 1a. It is seen that 52 per cent of both the older and the younger hypertensive persons (Groups 1 and 2) stated that they were unusually highstrung their whole life, compared to only 3 and 6 per cent of the corresponding control groups (3 and 4). Of the older group, 43 per cent, and of the younger, 53 per cent stated that they were unusually quick tempered their whole life, compared to only 3 and 13 per cent for the replies of the corresponding control groups. Of the older group, 69 per cent, and of the younger, 66 per cent said that they were unusually sensitive their whole life, compared to 9 and 18 per cent for the replies of the corresponding control groups. Of the older group, 70 per cent, and of the younger, 58 per cent said they worried unusually easily over little things their whole life, compared to only 11 per cent of the corresponding control groups. Of the older patients, 94 per cent, and of the younger, 69 per cent said that, compared to the average person their own age, they were definitely more active physically their whole life, compared to 13 and 10 per cent for the answers of the corresponding control groups. This unquestionable preponderance of high percentages among the hypertensive groups is seen also in the answers to practically all the other questions (Table 2).

Referring to Table 3 it is seen that the frequency of the various

traits in the hypertensive patients becomes exceedingly high when the replies to two or more questions are added together. Thus, for example, 97 per cent of the older and 70 per cent of the younger hypertensive patients said they were either unusually highstrung, or unusually active, or both, compared to 7 and 15 per cent for the replies of the corresponding control groups. This was one of the outstanding correlations of the entire study. Further correlations of combined questions are seen in Table 3.

TABLE 2.—PERCENTAGE INCIDENCE OF CERTAIN PERSONALITY CHARACTERISTICS IN SUBJECTS WITH HYPERTENSION AND WITH NORMAL BLOOD PRESSURE.

Group No.	Blood pressure.	Average age.	Number of patients.	Unusually highstrung.	Unusually quicktempered.	Unusually easily excited within themselves.	Unusually sensitive.	Unusually easy blushing.	Unusually easy embarrassment.	Unusually easy worrier.	Unusually serious.	Unusually shy.	Unusually fast walker.	Unusually fast worker.	Unusually fast talker or eater.	Unusually active physically.	Frequent epistaxis.	Hands or feet easily cold.	Family history of vascular disease.
1 . . .	H*	54	41	52	43	54	69	65	48	70	59	70	58	87	64	94	2	13	71
1a . . .	H	56	20	30	25	25	25	35	35	30	50	..	60	65	50	70	40
2 . . .	H	26	34	52	53	64	66	38	44	58	61	58	58	79	68	69	6	17	77
3 . . .	N	47	35	3	3	6	9	21	23	11	19	44	29	33	28	13	6	11	25
4 . . .	N	25	52	6	13	12	18	25	11	11	23	21	29	29	24	10	0	20	62

* Abbreviations in all the tables are the same. H = hypertension. N = normal.

TABLE 3.—PERCENTAGE INCIDENCE OF CERTAIN PERSONALITY CHARACTERISTICS IN SUBJECTS WITH HYPERTENSION AND WITH NORMAL BLOOD PRESSURE.*

Group No.	Average age.	Number of patients.	Unusually highstrung or quicktempered, or easily excited within themselves.	Unusually quicktempered or sensitive.	Unusually serious or sensitive.	Unusually sensitive or quick worker.	Unusually quicktempered or quick worker.	Unusually highstrung or active.	Unusually easy blushing or shyness.	Unusually quicktempered, or sensitive, or serious or active.
1 . . .	54	28	68	77	85	93	91	97	90	90
1a . . .	56	20	50	40	60	80	70	75	..	80
2 . . .	26	28	76	74	81	90	80	76	70	
3 . . .	47	31	3	9	25	36	30	7	39	35
4 . . .	25	46	12	29	35	41	36	15	33	

* Figures obtained by adding together the positive replies to two or more questions.

Turning next to Group 1a in Table 2, consisting of the specially selected, symptomless hypertensive subjects, it is first seen that to

every question there was also a definitely higher percentage of positive answers than in both control groups. However, compared to the other hypertensive groups (1 and 2), Group 1a had a much lower number of positive answers to the questions dealing with the emotional responses such as quick temper and sensitiveness. On the other hand, to the questions relating to physical activity, the symptomless hypertensive patients gave almost as high a percentage of positive answers as the other hypertensive groups.

Discussion. The present study confirms the often mentioned clinical impression that persons with arteriolar (essential) hypertension tend to have certain emotional and physical reactions much more frequently and intensely than comparatively healthy people of the same age group and with normal blood pressure—in the present study from 2 to 17 times as commonly as do the normal controls (Tables 2 and 3). The results confirm the author's previous impressions that hypertensive patients tend to be emotionally hyperactive, physically hyperactive, or both. In presenting and discussing the statistical data in Tables 2 and 3, the author has had only one purpose—to indicate trends rather than immutable statistics. Thus, the results in Tables 2 and 3 indicate that hypertensive patients tend to be highstrung individuals who either display quick temper or are easily excited within themselves. They tend to be unusually sensitive, being hurt by little things. In youth and often persisting to later life, they tend to blush easily, to be easily embarrassed, and to be unusually shy. In dealing with the events of life, however minute, they tend to be unusually serious and worry over trivialities. However, as seen in Table 2, a much smaller percentage of the symptomless hypertensive patients admit that they are emotionally hyperactive, although this percentage is definitely greater than in the control group. Physically, whether symptomless or not, the hypertensive individual seems to be an unusually rapid walker, even when in no special hurry. Hypertensive subjects tend to work at their tasks in home or in office with much more rapidity and thoroughness than the average person. They often tend to eat or talk rapidly. In general, they tend to be unusually active physically, in their domestic, occupational, and social activities. It cannot be too strongly emphasized that the author does not believe that every person with a hypertensive type of personality has or will develop arteriolar (essential) hypertension. Neither is it meant that every hypertensive patient has the type of personality above presented. It is clear, however, that most hypertensive patients in the groups studied are of the personality type described.

The Hypertensive Personality is of Lifelong Duration. Not only does the middle-aged hypertensive patient tend to be of a certain personality type, but the replies indicate that so far as he can remember he has always been of that type. It seems likely, there-

fore, that the hypertensive personality is present and recognizable in early life. This likelihood is further confirmed by the study of the younger hypertensive group, which already at an average age of 26 shows exactly the same type of personality reactions to life as the older group. The probability that most of the persons in our younger group with abnormally high blood pressure readings are cases of early arteriolar (essential) hypertension, is enhanced not only by the finding in them of a similar type of personality as in the older hypertensive patients, but also by the significant fact that about 80 per cent of them are the children of known hypertensive patients.

Differentiating the Hypertensive Personality from Other Types. It is important to distinguish the hypertensive personality from that present in anxiety-neurosis with normal blood pressure and in the manic-depressive type of individual. Thus, it is well known that hyperactive emotional responses are present in many nonhypertensive people who undergo marked emotional strain. In such people the emotional strain may cause not only hyperactive emotional responses, but also bodily symptoms—in other words the picture of the psychoneuroses. However, the difference between the hyperactive emotional responses of the hypertensive patients and of the psychoneurotic patients is usually one of duration—the personality type of the hypertensive person being lifelong, whereas in most psychoneurotics it is only as long as the existence of the emotional upset.¹³ Yet there are many psychoneurotic patients of almost lifelong duration. It is obvious, therefore, that a study such as this must try to avoid the use of subjects who have symptoms of psychoneuroses, or take account of it.

Therefore, as a control for this factor the personality of a group of symptom-free hypertensive individuals was studied. This group of 20 persons gave no history of symptoms suggesting psychoneurosis. They prided themselves on being unusually well all their lives and of practically never going to doctors. If it is true that many of the symptoms of hypertensive patients are due to emotional disturbances,¹³ it would seem likely that symptom-free hypertensive "patients" should have a less frequent incidence of traits associated with emotional instability than hypertensive patients with symptoms. This is exactly what was found in Group 1a. In these 20 symptomless hypertensive patients, only 30 per cent stated they were unusually highstrung compared to 52 per cent in the hypertensive patients with symptoms; 25 per cent said they were unusually quick-tempered, easily excited, or unusually sensitive, compared to 53, 64 and 66 per cent respectively in the symptom group. However, the hyperactive physical responses in the symptom-free group were as frequent as in the other hypertensive groups studied.

The hypertensive personality is quite different from that of the

neurasthenic individual. The latter, as a rule, may be emotionally hyperactive for a period, but is not physically hyperactive. He fatigues easily—one of the outstanding characteristics of the neurasthenic. He may want to do a great deal, but is unable to do so physically, which is in direct contradistinction to the hypertensive type.

The hypertensive personality must be distinguished also from the manic-depressive type. There are many people who will say that they are of the hypertensive type but have no hypertension. Many of these people, however, are of a manic-depressive type of personality without being psychotic. They have a great deal of physical energy and enthusiasm, but it is not a constant thing. Akin to the actual manic-depressive psychoses, they have periods in which they are unusually energetic, often lasting for months or more, followed by periods of depression during which their activity is much less. The hypertensive patient, however, has a drive within him which is persistent, steady, and not broken up by periods of depression. However, one cannot be dogmatic; for, mixed types often occur, and a hypertensive patient may have a depression.

Etiology of the Hypertensive Personality. This matter is unsettled. Moschcowitz⁵ believes it may be of environmental acquired origin, "the result of imitative tendency of children," which gives a pseudo-hereditary aspect to it. Against the environmental etiology of the hypertensive personality are 25 of the young control individuals in Group 4, who, although they are the children of hypertensive patients and they have lived in the environment of these parents and of their hypertensive brothers and sisters, have neither the hypertensive personality nor elevated blood pressure like their brothers and sisters. Barach,⁴ on the other hand, believes the hypertensive personality is primarily the result of physical influences, like the personality changes in myxedema, hyperthyroidism, or eunuchoidism. It is highly possible that the hypertensive personality is of physical, perhaps endocrine origin. Certain it must be, in the light of the present study, that the hypertensive personality, present as it is early in life, can be neither the result of any unusually high blood pressure, nor the result of secondary vascular disease. It is also unlikely that it is due to environmental imitation of parents.

Relation of the Hypertensive Personality to the Diagnosis of Essential Hypertension. The recognition of the hypertensive personality may be of definite aid in the diagnosis of arteriolar (essential) hypertension. Given a patient in whom the diagnosis of chronic vascular nephritis secondary to arteriolar hypertension is difficult to separate from a diagnosis of chronic glomerular nephritis with hypertension, the absence of the hypertensive personality is one more bit of evidence in favor of the primary kidney disease, rather than the hypertensive origin. The hypertensive personality type may also be of

aid in the diagnosis of early arteriolar hypertension; for, given a young person with mild fluctuating hypertension, the presence of the hypertensive personality, especially in the presence of a positive family history of vascular disease, strongly supports the diagnosis of early arteriolar essential hypertension rather than simple emotional hypertension. I believe that it is here that the knowledge of the hypertensive personality has one of its greatest applications—the early diagnosis of this disease. One may go even still further and say, as O'Hare¹⁴ has, that the presence of vasomotor instability (and I would add the hypertensive type of personality) in children of a hypertensive patient, even before the existence of hypertension, calls for prophylactic measures.

The Hypertensive Personality in Treatment of Arteriolar Essential Hypertension. Elsewhere I have described¹² the importance of attempting to modify the hypertensive personality in the treatment of arteriolar essential hypertension. The relation of the hypertensive personality to the production of early symptoms has already been discussed,¹³ so that therapy of early symptoms must take account of this fact. Suffice it here to say, that it is well known that the hyperactive emotional and physical responses of the hypertensive patient are accompanied by marked elevations in blood pressure. Therefore, any rational therapy of arteriolar essential hypertension must attempt to modify this personality, either by education, sedatives, or both.

Finally, it is sincerely hoped that the present study will stimulate further investigation of the hypertensive personality by specially trained students of personality.

Summary and Conclusions. 1. A simple study of the personality of 182 subjects has been made. These subjects consisted of middle-aged hypertensive patients, hypertensive patients between the ages of 18 to 35, middle-aged normal subjects with normal blood pressure, and young normal subjects with normal blood pressure.

2. The results indicate that hypertensive subjects tend to have a distinct type of personality. Their personality is characterized by increased psychomotor activity. They are dynamic, hyperactive individuals, with a large and steady output of energy. They tend to be sensitive and quick-tempered. The mood fluctuations, however, are not an important feature, which differentiates them from the manic-depressive individuals. The hypertensive personality has existed as far back as the subject can remember.

3. The relation of the hypertensive personality to the diagnosis and treatment of arteriolar essential hypertension is discussed.

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THE FRACTIONAL PHENOLSULPHONEPHTHALEIN TEST IN BRIGHT'S DISEASE.

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SINCE the introduction of the phenolsulphonephthalein test of kidney function by Rowntree and Geraghty⁹ the method commonly used has been the estimation of the dye excreted in specimens of urine collected 1 and 2 hours after injection. The value of this test in severe nephritis has been generally recognized. However, Christian and O'Hare³ and others have observed that this test fails to reflect the impaired function in moderate or slight degrees of nephritis, and they place more reliance on the 2-hour concentration test. In cases of mild or suspected nephritis Bowen² found the phenolsulphonephthalein test less informative than tests of urea excretion. Van Slyke, McIntosh, *et al.*¹³ have recently concluded that the urea clearance test shows diminution of renal function before the phenolsulphonephthalein test.

Rowntree, in 1910, stated that the "curve of elimination of phenolsulphonephthalein in nephritis differs from the normal in that the maximum intensity is slowly reached." Later Snowden¹² noted that the earliest indication of impaired renal function was a delay in the excretion of dye. Thus a patient with Bright's disease may have a total output of 60 per cent in 2 hours with only 30 per cent appearing in the first hour, whereas in the normal person 50 per cent appears in the first hour. In 1925 Shaw¹¹ determined the

normal curve of dye elimination by collecting urine at 5- and 15-minute intervals after intravenous injection and found that an average of 40 per cent of the dye appeared in the first 15 minutes. He applied this technique of fractional collections to cases of renal disease and found marked abnormalities in the curve of excretion in many cases where the 2-hour output was normal. A decreased output in the first 15 minutes or a delay in the peak of elimination was frequently the only evidence of kidney disease.

It is surprising that this important modification has had clinical application, to our knowledge, only in urologic surgery. We have employed Shaw's method of frequent collections, which we have called the *fractional phenolsulphonephthalein test*, in order to determine whether or not it gives a better indication of kidney function in Bright's disease than the usual method of hourly collections, and also to determine its comparative value with the urea clearance test.

The Excretion of Phenolsulphonephthalein in Normal Individuals. Chart 1, Fig. 1, indicates the variations of the curve of phenolsulphonephthalein excretion which we have obtained from 40 tests on 20 normal individuals ranging in age from 11 to 40 years. Two tests were done on each at an interval of several days. The subject voided, drank 600 cc. of water and after 30 minutes 1 cc. (6 mg.) of phenolsulphonephthalein was injected intravenously. Voided specimens of urine were then collected at intervals of 15, 30, 45, 60 and 120 minutes. Estimations of the per cent of dye excreted were made with a Duboscq colorimeter, using standards freshly prepared with phenolsulphonephthalein.

Except for the slightly lower average 15-minute output, this curve (Fig. 1) is similar to that described by Shaw. Seven initial readings were above 40 per cent and 3 were below 30 per cent. Eight individuals who doubled their fluid intake on the second test showed no greater variation in their curve than those on a constant intake. This agrees with the findings of Rowntree and Shaw but not with those of Sugimura,¹⁰ who noted an increase of about 5 per cent in the first 30 minutes' excretion while the subjects were forcing fluids.

Snowden has stated that the excretion of phenolsulphonephthalein is definitely increased in severe nephritis when the urine volume is increased. To estimate the effect of an increase in urine volume on the output of dye by such diseased kidneys we have repeated the fractional phenolsulphonephthalein tests on 4 patients with Bright's disease while they were forcing fluids. Under these conditions we find no significant changes in the dye output.

The Fractional Phenolsulphonephthalein Test in Bright's Disease. In the past 2 years we have used this test in a large number of patients with suspected renal disease. From this group we have selected all cases with a clinical diagnosis of Bright's disease in whom both the fractional phenolsulphonephthalein and the urea

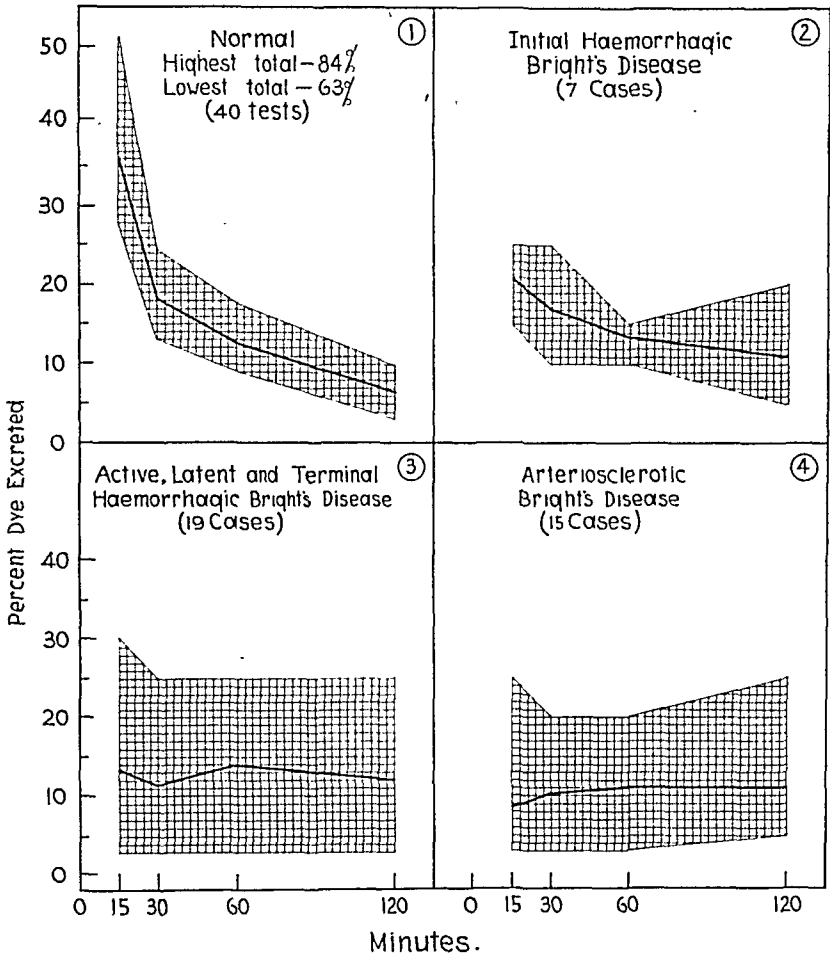


FIG. 1.—The variations and the average curve of phenolsulphonephthalein excretion in normal persons and in those with Bright's disease.

TABLE 1.—THE RELATION OF URINE VOLUME TO THE OUTPUT OF DYE BY DISEASED KIDNEYS.

No.	Fluid intake, cc.	Fractional 'phthalein.				Total.	Total urine volume, cc.	Date.
		Per cent dye.						
		Minutes.						
		15	30	60	120			
32	400 1200	10 5	10 10	15 15	25 12	45 42	275 770	2- 4-32 2-15-32
36	400 1500	10 10	5 5	10 10	5 15	30 40	175 515	2-12-32 2-15-32
22	400 1600	5 5	3 5	5 10	5 10	18 30	410 1275	2-15-32 2-16-32
17	600 2000	10 15	5 5	10 5	15 12	40 37	170 785	4-25-32 4-27-32

clearance tests were performed. No patients with congestive cardiac failure or with extrarenal factors, such as liver disease,⁴ or the recent ingestion of magnesium sulphate* were included.

Forty-three such cases are grouped according to the Addis classification of Bright's disease¹ as follows: hemorrhagic, 26; arteriosclerotic, 15; degenerative, 2.

We have divided hemorrhagic Bright's disease into 2 groups in the tables. The first group corresponds to acute glomerular nephritis and the second to the chronic form. Arteriosclerotic Bright's disease includes all cases in which the lesion is essentially vascular and thus includes the malignant hypertension of comparatively young people, of which there are 7 cases in our group of 15. Degenerative Bright's disease corresponds to lipoid nephrosis, amyloidosis and the nephritis of chemical and toxic poisoning.

Analysis of Data.—In the tables we have listed the significant urinary findings, the range of specific gravity, the blood non-protein nitrogen and the 2 tests done on each patient. The specific gravity was obtained in most instances from concentration tests, but in a few, further information of the ability of the kidney to concentrate the urine was gained from single urine examinations.

The urea clearance tests were performed according to the method described by Moeller, McIntosh and Van Slyke.⁷ The values for the 2 specimens of urine usually checked within 10 per cent and corrections for body weight⁸ were made for children. The normal range of this test in the standard clearance (where the urine volume is less than 2 cc. per minute) is from 76 to 121 per cent, so that any figure below 76 per cent indicates diminished renal function. In the maximum clearance (where the urine volume is above 2 cc. per minute) the normal range lies between 85 and 132 per cent.

The fractional phenolsulphonephthalein tests were done as part of the routine laboratory work, using Hynson, Westcott and Dunning standards, and the same technique was used as described for the normals except that the patient drank 400 to 500 cc. of water and the 45-minute specimen was omitted. Only occasionally was a patient unable to void at the stated intervals. No normal person excreted less than 28 per cent of dye in the first 15 minutes, but we have taken 25 per cent as the lowest limit of normal in the patients. Although the lowest total output in 2 hours in the normal group was 63 per cent, we have considered 55 per cent as normal in our analysis of cases for two reasons: (1) This is generally accepted; (2) Van Slyke *et al.* used this figure in their comparison of the urea clearance with the phenolsulphonephthalein test.

Analysis shows that there is some agreement of the range of specific gravity and the non-protein nitrogen with the urea clearance

* Macht⁶ has shown that the ingestion of magnesium sulphate delays the elimination of phenolsulphonephthalein, the effect lasting 3 to 4 hours after ingestion.

and fractional phenolsulphonephthalein tests. In the 43 cases we find that the specific gravity was below 1.024 in 21, the non-protein nitrogen was above 40 mg. per 100 cc. in 25, the urea clearance test indicated impaired renal function in 29 cases and the fractional phenolsulphonephthalein in 35. Inasmuch as we are primarily interested in the fractional phenolsulphonephthalein and the urea clearance tests, we shall consider only these two.

TABLE 2.—INITIAL HEMORRHAGIC BRIGHT'S DISEASE.

(Cs Indicates Standard Urea Clearance; Cm Indicates Maximum Urea Clearance.)

No.	Sex, age.	Urine.					Fractional 'phthalein.					Urea clearance, per cent of normal av.		
		Alb.	R.B.C.	Casts.	Range of sp. gr.	NPN.	Percent excreted.				Date.	Date.		
							Minutes.						Total.	
							15.	30.	60.	120.				
1	F 37	+	+++ ○	+	1.010 1.018	32	25 30	10 18	15 15	10 10	60 73	5-16-31 5-24-32	51% Cm 94% Cs	5-25-31 6-10-32
2	M 15	+++	++	+	1.010 1.028	41 27	20	25	15	15	75	3-10-31	144% Cm	3-18-31
3	M 6	++	+++	+++	1.012 1.024	46 39	20	25	15	.	60 (1 hr.)	5-28-31	42% Cs	5-27-31
4	M 14	++++ ++++	++++ ++++	++++ ++++	1.014 1.026	27 35	20 20 17	25 20 23	15 10 15	5 5 .	65 55 55 (1 hr.)	1-27-32 2-19-32 7-22-32	135% Cs 135% Cs 116% Cm	1-29-32 2-25-32 7-22-32
5	M 43	++ ++	+++ +	++++ ++	1.010 1.034	85 35	20 25 23	15 15 25	15 13 15	12 10 10	60 63 73	5-27-30 6-18-30 7-17-30	48% Cs 47% Cm	5-28-30 6-24-30
6	M 15	+	++	+++	1.003 1.024	34 23	20	15	15	20	70	12-19-30	107% Cs	12-18-30
7	M 14	++++ ○	++++ +	++ +	1.010 1.020	104 60 34	15 30	10 15	10 ..	5 ..	40 45 (½ hr.)	11-1-31 11-15-31	50% Cs 122% Cs	11-2-31 11-18-31

In Table 2 (initial hemorrhagic Bright's disease) the first 6 of the 7 cases had an output of phenolsulphonephthalein of at least 55 per cent in 2 hours. This would be considered normal if it were the only information we had concerning the excretion of the dye. However, using the fractional method, we find that there is a delay in the elimination of the dye, which we interpret as indicating diminished kidney function, in all of these except Case 1, whose 15-minute excretion was 25 per cent. In only 3 of the 6 (Nos. 1, 3, 5) did the urea clearance indicate impaired function. In 1 case (No. 1) the urea clearance alone indicated diminished function, but a year later both tests gave higher values.

Case 7, a boy, aged 14 years, entered the hospital in convulsions. Both the fractional phenolsulphonephthalein and the urea clearance

tests, performed several days later when he was able to coöperate, were below the normal variations. Two weeks later when he was clinically improved and albuminuria had disappeared, both tests had returned to normal.

TABLE 3.—ACTIVE, LATENT AND TERMINAL HEMORRHAGIC BRIGHT'S DISEASE.

No.	Sex, age.	Urine.				NPN.	Fractional 'phthalein.					Urea clearance, per cent of normal av.		
		Alb.	R.B.C.	Casts.	Range of sp. gr.		Per cent dye.				Date.		Date.	
							Minutes.							Total.
							15.	30.	60.	120.				
8	M 49	+++ ++	++++ ++++	++ ++	1.005 1.019	40 ...	25 25 25	25 .. 15	15	10 .. 15	75 .. 55	1-10-32 1-14-32 7-1-32	130% Cm 98% Cs	1-14-32 7-11-32
9	F 33	+++	+	+	1.018 1.024	26	25	20	20	10	75	6-12-32	76% Cs	6-14-32
10	M 50	+++	+	++++	1.015 1.024	29	25	15	15	5	60	11-1-31	85% Cs	11-10-32
11	M 40	++++ ++++	++ ++	++++ ++++	1.018 1.026	35	30 8	10 12	10 18	10 15	60 53	12-9-31 6-3-32	93% Cs 53% Cs	12-10-31 7-1-32
12	M 26	++++	+++	++	1.010 1.020	26	20	15	15	15	65	10-10-30	39% Cs	11-6-30
13	F 38	○ +	+	+	1.006 1.025	53 46	10 20	10 10	20 20	25 ..	65 50 (1 hr.)	5-16-31 8-19-32	51% Cm 92% Cs	5-21-31 9-9-32
14	F 15	++++	+	+++	1.012 1.022	39 59	10	15	15	20	60	12-19-30	50% Cs	12-19-30
15	F 27	+	+	○	1.002 1.014	72 41	15	..	25	15	55	3-20-31	23% Cm	4-6-31
16	F 14	++++	+	+++	1.008 1.024	35	10	15	15	15	55	12-27-31	51% Cs	12-24-31
17	M 53	++++	+	+	1.016 1.022	36 ..	15 10 8	13 5 12	15 10 15	15 15 ..	58 40 35 (1 hr.)	4-21-32 4-25-32 6-20-32	80% Cs 104% Cm	4-22-32 7-1-32
18	F 20	++++ ++++	++ +	++++ ++	1.010 1.030	29 ..	15 5	15 10	15 15	.. 15	45 (1 hr.) 45	12-16-31 7-7-32	77% Cs 91% Cs	12-2-31 7-8-32
19	F 22	++	○	+	1.010 1.018	44	17	10	15	.. 37 (1 hr.)	37 (1 hr.)	6-4-32	50% Cs	6-6-32
20	M 30	+++	++++	++++	1.010 1.024	48 31	3	5	25	10	43	3-19-32	89% Cs	3-9-32
21	F 15	++++	+	++++	1.014 1.032	25 44 63	5	5	8	8	26	11-2-31	41% Cs	12-9-31
22	F 25	++	+	+	1.010 1.020	38 ..	3 5	5 3	3 5	8 5	19 18	1-22-32 2-15-32	44% Cm	2-3-32
23	F 59	++++	○	++++	1.012 1.024	60 50	3 ..	3 ..	3 ..	3 ..	12 ..	11-29-31	18% Cs Died	12-2-31 9-10-32
24	F 44	+	+	+++	1.010 1.014	95 70	0 ..	0 ..	0 ..	0 ..	0 ..	6-17-31	10% Cs Died	6-10-31 7-13-31
25	M 23	++++	++	++++	1.010 1.020	70 ..	5 ..	5 ..	5 ..	10 ..	25 ..	9-21-31	18% Cs Died	10-14-31
26	M 17	++++	+	++	1.008 1.015	180 ..	0 ..	3 ..	3 ..	3 ..	9 ..	3-11-32	8% Cs Died	3-14-32 4-14-32

The tests in Case 4 are interesting because the patient entered in the initial stage and progressed into the active chronic stage with persistence of hematuria and albuminuria. During this time 3 comparative tests were done. The fractional phenolsulphonephthalein tests showed progressive impairment whereas the urea clearance remained normal.

TABLE 4.—ARTERIOSCLEROTIC BRIGHT'S DISEASE.

No.	Sex, age.	Urine.				NPN.	Fractional 'phthalein.					Urea clearance, per cent of normal av.		
		Alb.	R.B.C.	Casts.	Range of sp. gr.		Per cent dye.				Date.		Date.	
							Minutes.							Total.
							15.	30.	60.	120.				
27	F 35	+	○	○	1.006 1.020	37 27	25 ...	20 ...	20 ...	15 ...	80	5-27-31	57% Cs Died	5-27-31 3-3-32
28	F 29	+++ +++	○ ○	++ ○	1.010 1.030	59	8 tr	15 3	8 5	20 5	51 15	11-30-30 6-27-32	59% Cs 35% Cs	12-1-30 6-27-32
29	F 67	++	++	+++	1.010 1.018	76 60	15	10	15	10	50	5-14-31	52% Cs	5-15-31
30	M 50	+	○	+	1.018 1.028	38	12	15	15	10	52	11-3-30	65% Cs	11-5-30
31	F 36	++	○	++	1.013 1.020	25	8	20	10	10	48	11-11-30	79% Cm	11-17-30
32	M 38	+++	+	++	1.010 1.016	36 65	15 10	20 10	10 25	45 45 10	1-29-32 2-4-32 3-22-32	63% Cs 35% Cm Died	2-4-32 3-22-32 6-1-32	
33	F 50	++	○	○	1.006 1.020	83 50	5	10	15	15	45	3-14-31	31% Cs	3-16-31
34	M 47	+++	+	+	1.012 1.024	45 64	5	15	10	10	40	1-17-31	72% Cs	1-13-31
35	F 22	+++	+	+	1.008 1.025	22	10	5	10	10	35	10-9-30	37% Cs Died	10-10-30 12-13-30
36	F 45	+++	+	○	1.001 1.016	46	5	5	5	10	25	6-14-32	70% Cs	6-13-32
37	F 82	+++	○	+	1.010 1.020	64 ..	3 ..	3 ..	3 ..	5 ..	14 ..	2-5-32	39% Cs Died	2-8-32 7-22-32
38	M 40	+++	+	++	1.008 1.024	47 59	10 ..	5 ..	10 5	5 13	30 18	2-12-32 4-2-32	122% Cs 67% Cs Died	2-15-32 4-5-32 6-27-32
39	F 41	++	+	+	1.012 1.024	36	15	15	10	15	55	10-29-30	50% Cs Died	11-12-30 3-31-31
40	F 55	++	+	++++	1.014 1.020	66 ..	3	5 ..	5 ..	13 ..	12-16-31	15% Cs Died	12-21-31 3- -32
41	F 49	+++	+	++	1.009 1.012	130 ..	3 ..	0 ..	3 ..	3 ..	9	12-14-31	7% Cs Died	12-14-31 5- -32

From Table 3 we find that the first 10 patients (Nos. 8 to 17) had at least 55 per cent output in 2 hours; 6 of these (Nos. 12 to 17) showed abnormal fractional tests, with a delay in the excretion

of dye. The remainder of the group (Nos. 18 to 26) all showed rather marked kidney impairment by the fractional test and the total output was well below 55 per cent. In all except 3 of the patients (Nos. 17, 18, 20) both the urea clearance and the fractional phenolsulphonephthalein tests agreed. In these only the latter test indicated a diminished function. We have been able to repeat the tests at intervals of several months on Patients 8, 11, 13, 17 and 18. In Patient 8 the tests were normal on both occasions, although albuminuria and hematuria were still present at the second examination. The first fractional phenolsulphonephthalein and urea clearance tests were normal on Patient 11, although at that time the patient had considerable edema, albuminuria and a blood pressure of 160 systolic and 100 diastolic. Six months later both tests showed a marked decrease. The total output in the dye test was very little changed, but the fractional readings showed a great difference with a low initial output and a delayed excretion. In Patient 13 both tests showed improvement after a year's interval. Patient 17 showed a slight decline in the fractional test alone. Patient 18 showed a decrease in the fractional phenolsulphonephthalein but the urea clearance increased 14 per cent. Clinically this patient was worse and was having persistent edema to the mid-thighs at the time of the second test.

Of the patients with arteriosclerotic Bright's disease (Table 4) only 2 (Nos. 27, 39) had a total output over 55 per cent. In Patient 39 the excretion of dye was delayed, but in Patient 27 it was normal by the fractional test, yet the urea clearance showed an impaired function.

TABLE 5.—DEGENERATIVE BRIGHT'S DISEASE.

Case 42.—Diagnosis: amyloidosis; tuberculosis of the cecum.

Case 43.—Diagnosis: bichlorid of mercury nephrosis.

No.	Sex, age.	Urine.				N.P.N.	Fractional 'phthalein.				Urea clearance, per cent of normal av.		
		Alb.	R.B.C.	Casts.	Range of sp. gr.		Per cent dye.				Date.	Date.	
							Minutes.						Total.
							15	30	60	120			
42	M 25	++++	0	++++	1.008 1.022	24	15 10	30 10	15 20	60 (1 hr.)	12-12-31 12-18-31	102% Cs	12-7-31
43	M 39	++	0	+	1.005 1.021	30	15 20	35 35	15 17	65 75	5-28-32 6-3-32	96% Cs	5-31-32

Comparative tests done after a lapse of months in Patients 28 and 32 showed a diminished kidney function by both tests, although a greater diminution was reflected by the fractional phenolsulphone-

phthalein. In Patient 38 the urea clearance test at the first period of study showed a high normal but a very low fractional phenolsulphonephthalein test. Two months later the patient became much worse and the urea clearance was reduced one-half. He died shortly thereafter.

The effect of a high blood pressure on the excretion of phenolsulphonephthalein remains an unsettled problem. Lundsgaard and Moeller⁵ believe that the dye output may be decreased in the presence of a high blood pressure. We have encountered patients with hypertension without congestive failure who had depressed curves of phenolsulphonephthalein excretion but with few or no other signs of kidney disease. However, we have observed normal fractional phenolsulphonephthalein tests in as many patients with hypertension in whom there was no evidence of Bright's disease.

In Table 5 are listed the 2 cases of degenerative Bright's disease. In both of these there was a delay in the elimination of phenolsulphonephthalein, yet the total output of the dye and the urea clearance were normal.

Discussion. In summing up we find that 14 patients (32.5 per cent) with a total dye output of 55 per cent or more had a delay in the elimination of phenolsulphonephthalein. This group represents cases that would be judged to have a normal excretion of dye by the old method of hourly collections, but this delay shown by the fractional method indicates a diminished renal function. The charts in Fig. 1 show the variations and the average curve of dye excretion in normal persons and in those with Bright's disease. As the renal lesion progresses it is apparent that the curve tends to flatten out.

In a comparative study of the urea clearance test with the 2-hour output of phenolsulphonephthalein after intravenous injection, Van Slyke *et al.* have shown that when the urea clearance is between 40 and 60 per cent of normal average function about one-half the phenolsulphonephthalein outputs are above and one-half below 55 per cent of the dye injected. We find this to be true of our cases, but an analysis of the 8 cases (Nos. 1, 3, 5, 13, 14, 16, 27, 39) with the phenolsulphonephthalein output above 55 per cent and the urea clearance between 40 to 60 per cent shows that all but 2 (Nos. 1, 27) had a delayed excretion of dye indicating impairment of kidney function and thus agreeing with the urea clearance test. On the other hand, there were 9 patients (Nos. 2, 4, 6, 17, 18, 20, 38, 42, 43) in whom the urea clearance was 76 per cent or above and yet the fractional phenolsulphonephthalein test showed a diminished function.

Of the 12 patients in whom repeated tests were done later in the course of their disease we find that 5 (Nos. 7, 11, 13, 28, 32) had approximately parallel changes in both the urea clearance and the

fractional phenolsulphonephthalein tests. In 3 (Nos. 4, 17, 18) a decrease in the kidney function of patients with active hemorrhagic disease was shown only by the phenolsulphonephthalein test. In 2 (Nos. 1, 5) the urea clearance gave a better indication of the changes in function. In 1 (No. 8) both tests were normal.

It is particularly significant, on review of all cases, that an abnormal elimination of the dye was reflected chiefly in the first 15-minute specimen, and so this is by far the most important. For the general practitioner and in the out-patient department this determination alone would be sufficient in most cases. It is, of course, essential to know that there is no urinary retention and that the patient has completely emptied the bladder. Finally it should be emphasized that the fractional phenolsulphonephthalein test is a simple procedure, not requiring the aid of a chemical laboratory, and in our experience is more practical than the urea clearance test.

Summary and Conclusions. The fractional method of estimating the elimination of phenolsulphonephthalein (15, 30, 60 and 120 minutes) has been studied in the past 2 years in 20 normal subjects and a large number of patients with suspected renal disease.

We have found that in Bright's disease the fractional test may show evidence of impaired renal function when the test as usually done, with hourly collections, is interpreted as normal.

This fractional test is quite as informative as the urea clearance test and reflects the diminishing function in progressive kidney disease.

Since it is easier to perform, it is the method of choice for routine clinical work.

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NORMAL VARIATIONS IN RENAL FUNCTION TESTS WITH DISCUSSION OF THEIR PHYSIOLOGIC SIGNIFICANCE.

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IN order to estimate the value of kidney function tests in renal disease it is important to know what function of the kidney each test measures and how great a departure from normal must occur before abnormal function can be revealed. Most tests in clinical use today are able to indicate at best gross damage to the kidney, and physicians make little attempt to separate them according to the type of disturbed kidney physiology. Albuminuria, for example, is due to a different physiologic mechanism than is an inability of the kidney to concentrate urine, but both abnormalities frequently are interpreted as signs of nephritis without thought as to their underlying cause.

One great obstacle to the scientific classification of renal function tests is the delay in accepting the Ludwig theory of urine formation of filtration through the glomeruli with a reabsorption of fluid and solids in the tubules, as set forth by Cushny¹ and verified by the direct observations of Richards and his colleagues.² According to this theory, which we have adopted as a working hypothesis, in the glomeruli a process of filtration takes place whereby all of the constituents of the blood plasma except the proteins pass into the glomerular filtrate in the same concentration as they exist in the plasma. As this filtrate passes down the tubules most of the water is reabsorbed into the blood. The solid waste elements of the filtrate return through the tubular walls in greater or less extent. Thus creatinin, to which the tubular cells are apparently impermeable, probably is not appreciably reabsorbed, whereas about 50 per cent of the urea is reabsorbed. Certain substances present in the plasma, however, normally appear in the urine either not at all or in less concentration than in the plasma. These elements, such as glucose and chlorids, known as threshold substances, cannot be reabsorbed in the tubules by a simple process of back diffusion, but by a specific activity of the tubular cells.

In order to account for the degree of concentration of some of the substances in the urine of man, Rehberg³ has calculated that a

glomerular filtration of from 100 to 200 cc. per minute is necessary. Since the urinary output under normal conditions rarely exceeds 1 to 2 cc. per minute, it is obvious that about 99 per cent of the water may be reabsorbed by the tubules. To estimate the amount of glomerular filtration Rehberg employs creatinin as an index, since there is indirect evidence that little or none of this substance is reabsorbed in its passage down the tubules. If the concentration of creatinin in the blood and urine and the urinary excretion per minute are known, then, as creatinin concentration in the glomerular filtrate and plasma is identical,² the ratio of the percentage of urine creatinin to plasma creatinin represents the degree to which the glomerular filtrate is concentrated. This value is known as the *concentration index*. The amount of glomerular filtrate formed per minute is, therefore, equal to this concentration index times the urinary excretion and can be determined from the formula:

$$\text{Glomerular filtrate} = \frac{\text{urinary concentration creatinin}}{\text{plasma concentration creatinin}} \times \text{urine formed per minute.}$$

Under abnormal conditions, alterations in the formation of urine may occur from disturbances of: (1) filtration and (2) reabsorption. In studying the function of the kidneys clinically, it is desirable to obtain a separate estimate of these two functions. Filtration may be lessened by: (a) Diminution in the glomerular blood pressure; (b) a decrease in permeability of the glomerular membrane; or (c) a reduction in cross-sectional area of the filtering surface due either to damage to individual glomeruli or to a reduction in the total number of glomeruli. Reabsorption of fluid may be lessened either because of an increased volume of filtrate flowing down the tubule or as a result of damage to the tubular cells.

Clinical Methods for Determining Altered Renal Function. 1. *Glomerular Function.* The creatinin clearance procedure of Rehberg gives a direct indication of the amount of glomerular filtration. The urea clearance test under conditions of maximal excretion also gives a relative index of the degree of filtration, since with urinary excretions exceeding 2 cc. per minute the percentage of back diffusion of urea through the tubules is nearly constant. When the urea and creatinin clearance are performed simultaneously, it is possible to compute the percentage of urea reabsorbed by the tubules and thus detect any increased permeability which may occur.

In the advanced stages of renal disease the glomerular filtration is so much decreased that the kidneys are unable to maintain an adequate excretion of nitrogenous and other waste products. These substances are, therefore, found in abnormally high concentration in the blood plasma. In clinical practice the usual tests are for the total nonprotein nitrogen, urea nitrogen, creatin, creatinin and uric acid of the blood.

The presence of albumin in the urine indicates an abnormal permeability of the glomerular membrane to protein, and the presence of red blood corpuscles is due either to increased permeability or to rupture of capillaries. Casts are found as the result of inflammatory changes and are due to the coagulation of protein and cells which have passed into the lumina of the tubules.

2. *Tubular Function.* The ability of the tubules to reabsorb water is best measured by procedures which concentrate the urine to as high a degree as possible. The capacity of the tubular cells to absorb threshold substances actively can be examined by estimating the concentration of one or more of these solids in the blood and urine.

Purpose of Investigation. In order to correlate a study of several simultaneously applied clinical technical procedures with the physiologic functions which they estimate and to show how fluctuation in one test may affect the outcome of other tests, we have studied a group of normal young adults, none of whom had albuminuria or an abnormal urinary sediment.

Methods. The subjects were in a fasting state and remained in bed throughout the test periods except when the concentration tests were made.

(a) *Creatinin Clearance.* The technique of Rehberg³ with unimportant modifications was followed. Three grams of creatinin were fed 1½ hours before the urine collection period began. The plasma creatinin was determined by the method of Folin and Wu⁴ using picric acid purified according to Benedict's directions.⁵ The urine creatinin was determined by Folin's method.⁶ The calculation of the glomerular filtrate was made according to the formula previously stated. The values for plasma creatinin found in the samples taken before and after each hourly test period were averaged.

The terms "creatinin clearance" and "urea clearance" have been employed, because such a term was suggested by Van Slyke for the urea procedure and we have used his formulæ in expressing our values. The "creatinin clearance" is synonymous with the term "glomerular filtrate."

(b) *Urea Clearance.* This was usually determined simultaneously with the creatinin clearance. The analyses for urea were carried out on whole blood and urine by Van Slyke's gasometric extraction method.⁷

The urea clearance per minute when the urinary excretion exceeded 2 cc. per minute was calculated from the same formula as creatinin, substituting urea for creatinin. Seventy-five cc. was taken as the theoretical normal. This is called the "maximum clearance."

When the diuresis falls below 2 cc. per minute Van Slyke and his co-workers⁸ have suggested that the formula is best expressed by taking the square root of the urinary minute volume rather than the total urinary minute volume. This determination is called the "standard clearance." In the few cases (Table 1) where the diuresis fell below 2 cc. per minute, the actual urea clearance values were calculated from the formula for maximal clearance for the sake of uniformity. In these cases, however, figures for the percentage of normal in the same table were calculated from the standard clearance formula, taking 54 cc. as the theoretical normal.

(c) *Concentration Test.* A modification of the Volhard and Strauss tests for the concentration and dilution of urine similar to that suggested by Pratt⁹ was employed. The only fluid permitted was 1500 cc. of water

at the beginning of the test. The output in the first 4 hours, the total day and the total night outputs were determined and the specific gravities of the individual samples were measured.

TABLE 1.—THE VALUES OF THE CREATININ AND UREA CLEARANCES OBTAINED IN NORMAL INDIVIDUALS.

Subject.	Age.	Urine, cc. per min.	Creatinin.		Urea.			Blood urea nitrogen, mg. per cent.
			Conc. index.	Filtrate, cc. per min.	Clear- ance, cc. per min.	Per cent of normal.	Excre- tion,* per cent.	
1	31	0.76	179	136	56	118†	38	10.2
		1.40	89	125	69	108†	52	
2	44	2.42	60	135	61	81	39	15.2
		7.00	22	154	67	90	40	
3	31	4.75	36	172	112	149	60	7.4
		8.00	17	136	119	158	81	
4	22	8.93	17	154	70	93	42	9.0
		11.05	14	153	77	102	46	
5	41	0.40	301	120	34	99†	26	11.8
		2.25	57	129	70	94	51	
6	34	1.50	108	162	64	119†	44	11.5
		4.28	42	180	96	128	50	
7	26	2.17	67	145	68	91	43	9.0
		8.26	15	122	54	73	40	
8	38	7.50	16	117	48	64	37	7.9
		11.00	7	79	66	85	79	
9	35	7.09	20	141	80	108	53	15.6
		9.16	14	125	92	122	68	
10	29	1.28	125	160	64	105†	37	10.3
		3.50	49	170	81	108	43	
11	29	3.78	43	164	100	134	57	11.0
		4.67	31	146	98	130	61	
12	45	7.33	30	220	109	145	46	7.9
		6.57	29	180	97	129	47	
13	22	1.63	70	102†	..	8.9
		8.33	69	82	..	
14	24	5.66	63	85	..	13.2
		9.47	58	77	..	

* Calculated according to Rehberg,^{3,14} corrected for plasma urea nitrogen.

† Per cent of normal calculated by formula for "standard clearance" = $\frac{U\sqrt{V}}{B}$. All

the other per cents of normal are on a basis of "maximum clearance" = $\frac{U V}{B}$.

Results. Creatinin and Urea Clearance. Creatinin and urea clearance tests were carried out simultaneously in 12 subjects (Table 1). The creatinin filtrate varied from 117 to 220 cc. per minute with one exception probably due to technical error. These figures are in accord with Rehberg's and average slightly less than those given by Cope¹⁰ for 1 normal male.

In the same 12 subjects and in 2 more, urea clearance measurements were made. These varied from 48 to 119 cc. per minute. When expressed in terms of percentage of normal, assuming a maximum clearance of 75 and a standard clearance of 54 to be nor-

mal, the figures ranged from 64 to 158 per cent. In the cases with a clearance of 64 and 73 per cent, second determinations, respectively, showed 85 and 91 per cent of normal.

Although a rough parallelism was found to exist between the levels of the creatinin and urea clearance, this did not hold with any exactitude. Most of the discrepancy probably was due to the experimental error of the methods, but it is quite possible that fluctuations were caused by individual variations which permitted the urea to diffuse in different proportions back through the tubules to the blood.

Our observations are in agreement with Rehberg that the glomerular filtrate measured by the creatinin test is essentially constant irrespective of the urine volume. This constancy also holds for the urea clearance when the diuresis exceeds about 2 cc. per minute, as has been noted by Van Slyke.⁸ When, however, the diuresis falls below this rate the percentage excretion of urea becomes progressively less, with a consequent decrease in the urea clearance. Our observations also suggest that the percentage excretion of urea varies between individuals even under identical conditions.

In order to ascertain whether the oral administration of urea or creatinin increased the urea clearance values, 9 subjects were tested. The results (Table 2), in accord with those of Addis and Drury,¹¹ indicate that there is no tendency for either urea or creatinin to increase the urea clearance, or, by inference, the creatinin clearance either. There was some fluctuation in the consecutive hourly determinations in spite of the maintenance of conditions as constant as possible. This is particularly marked in Subject 19. In only 4 instances did the urinary output fall below 2 cc. per minute. This low urine output accounts for the low clearance values found in Subject 7 when urea was fed.

It is desirable in the carrying out of both the creatinin and urea clearance procedures in clinical practice to have conditions made as constant as possible. That is, an adequate diuresis of at least 2 cc. per minute should be insured by having the subject drink 400 cc. or more water each hour before and during the test periods. The patient should be kept quiet in bed and preferably should be in the fasting condition.

Concentrating Power of Tubules. Dilution concentration tests were carried out in 5 subjects (Table 3). Even with normally functioning kidneys the results may be modified by such factors as the position and activity of the individual, the degree of hydration or dehydration and the elimination of fluid by other channels. It is probable that one or more of these factors was responsible for the lack of urine dilution below a specific gravity of 1.007 in Subject 15, and for the failure of 3 of the 5 subjects (Nos. 10, 17 and 18) to excrete all or nearly all of the 1500 cc. of water ingested within 4 hours. For clinical purposes, however, the value of this

test consists not so much in the total urinary output or the hourly variation in it as it does in the range of specific gravity through which the urine varies and particularly in the maximum specific gravity to which the individual can concentrate urine. It is this that shows the capacity of the tubules to reabsorb water. Practically all normal individuals can concentrate urine to a specific gravity of 1.025 or more.

TABLE 2.—THE EFFECT OF FEEDING CREATININ AND UREA ON THE UREA CLEARANCE OF NORMAL INDIVIDUALS.

Subject.	Urea clearance.			Urine, cc. per min.
	Nothing fed. cc. per min.	Creatinin fed 3 gm. cc. per min.	Urea fed 30 gm. cc. per min.	
10	76	5.3
	80	4.9
		64	...	1.3
		81	...	3.5
			80	3.0
			77	5.7
12	102	3.8
	100	12.5
		109	...	7.3
		97	...	6.6
			92	2.3
			89	3.5
19	116	7.7
	73	2.3
		93	...	5.4
		77	...	2.5
			123	11.0
			83	6.8
11	93	12.1
	75	7.5
		98	...	4.7
		100	...	3.8
13	70	1.6
	69	8.3
			65	5.0
			60	12.3
			57	12.3
7		68	...	2.2
		54	...	8.3
			36	1.0
			38	0.9
8		48	...	7.5
		66	...	11.0
			62	9.0
			62	13.6
9		80	...	7.1
		92	...	9.2
			111	10.9
			83	12.0
			85	11.2
				5.7
14		63	...	5.7
		58	...	5.7
			57	4.4
			52	9.5
			48	8.8

TABLE 3.—THE RESULTS OF DILUTION-CONCENTRATION TESTS IN 5 NORMAL INDIVIDUALS, SHOWING VARIATION IN URINE OUTPUT, SPECIFIC GRAVITY, CONCENTRATION INDEX AND GLOMERULAR FILTRATE.

Sub- ject.	Age.	4-hour output, cc.	Day output, cc.	Night output, cc.	Total output, cc.	Specific gravity.		Concentration index.		Filtrate.	
						Low- est.	High- est.	Low- est.	High- est.	Low- est, cc.	High- est, cc.
10	29	685	925	410	1325	1.001	1.036	10	226	26	97
15	33	1030	1580	220	1800	1.007	1.030	16	243	74	180
16	25	1225	1390	285	1675	1.001	1.033	8	270	54	102
17	33	850	1190	340	1530	1.001	1.031	10	160	65	120
18	28	965	1220	380	1600	1.002	1.026	11	137	54	89

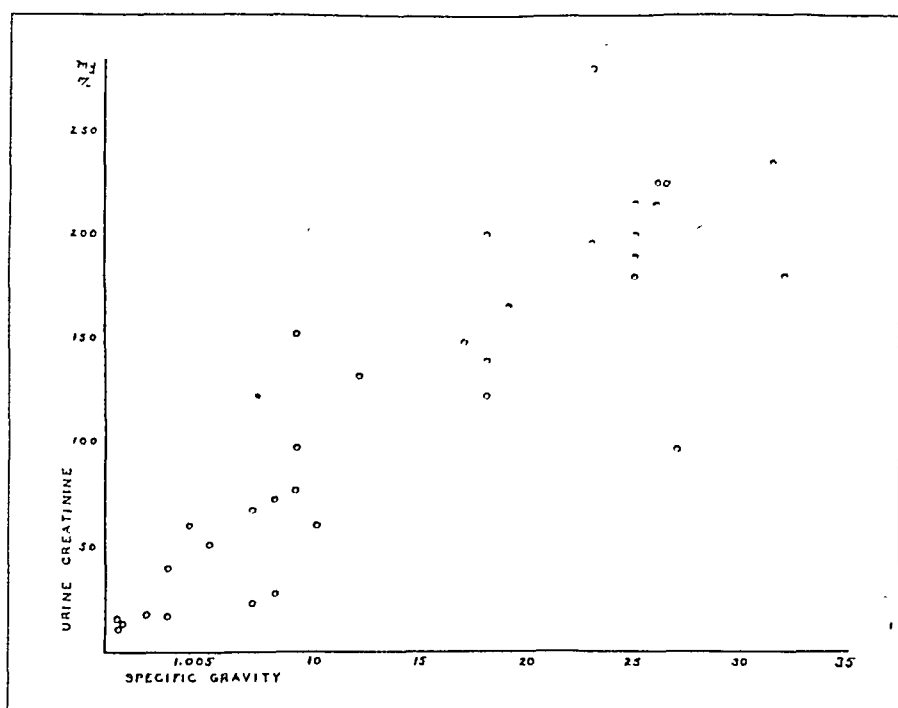


CHART I.—The relationship of the variation in urine specific gravity and creatinin concentration in normal individuals.

Daily Variation in Glomerular Filtrate. In conjunction with the dilution-concentration test, the glomerular filtration during each of the collection periods was calculated to ascertain what changes took place when urine was passed which varied from extreme dilution to marked concentration. No creatinin was fed. Only 1 blood creatinin determination was made in each subject. There is evidence that the percentage variation of the plasma creatinin in the same individual at different times is slight.¹² The relationship of the creatinin concentration in the urine to its specific gravity is

depicted in Chart I which shows that these two factors bear practically a linear relationship to each other. That is, under normal circumstances the specific gravity of the urine varies in direct proportion to the amount of creatinin present.

The low values obtained for the glomerular filtrate, we believe, are due largely to the experimental error in determining plasma creatinin at normal levels. Not only is it impossible to determine with accuracy the normal amount of plasma creatinin, but it is quite likely that the results obtained yield values in excess of the true amount.^{3,10,13} There is also some evidence that the glomerular filtrate tends to be somewhat higher when the subject is in the prone than in the upright position.¹⁴

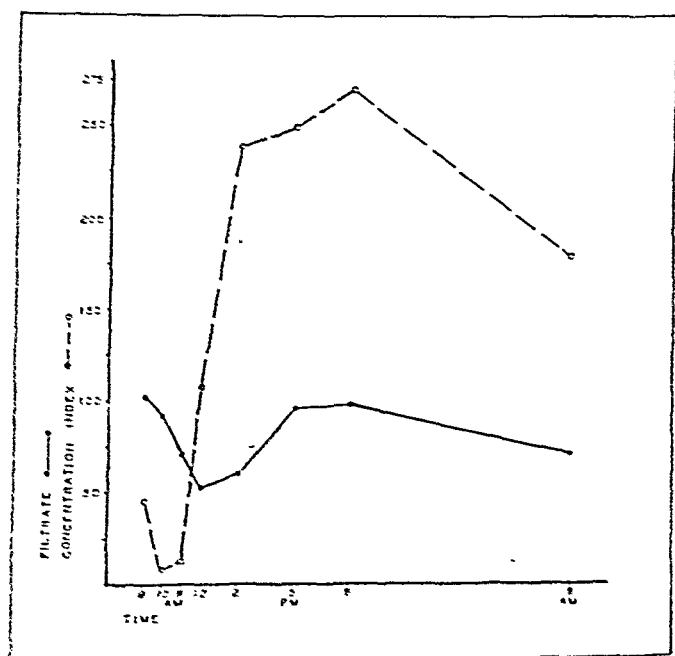


CHART II.—The diurnal variation of glomerular filtrate and of the concentration index during a dilution-concentration test in Subject 16.

Chart II and Table 3 show the relative constancy of the glomerular filtrate when compared with the change in concentration and amount of urine which was noted by Fremont-Smith¹⁵ and others. In other words, the variation in the amount of water excreted and in the concentration of urine is controlled largely by the extent of the reabsorption of water in the tubules.

Clinical Application of Renal Function Tests. No single technical procedure is adequate to test thoroughly the function of the kidney. Assuming the correctness of the filtration-reabsorption theory of

renal activity, it is possible to gain information concerning the following processes:

1. Permeability of glomeruli.
2. Glomerular filtration.
3. Tubular reabsorption of fluid.
4. Return of solids through the tubules into the plasma.
5. The "vital" reabsorption of threshold substances.

Except under unusual circumstances there is little value in testing the fourth and fifth processes in cases of inflammatory or vascular nephritis because rarely are they markedly abnormal. However, each of the first three kidney processes should be examined.

Information is gained regarding the permeability of the glomeruli by examination of the urine for albumin, red corpuscles and casts.

The urea or creatinin clearance tests are indices of glomerular filtration. Either test can be employed clinically. It should be appreciated that the reliability of the final results in these procedures is as much dependent on the accuracy in the collection of all the urine passed over an accurately timed period as on the laboratory analysis.

The tubular reabsorptive power is shown by concentration tests of which that of Vollhard is a representative example.

Determination of phenolsulphonphthalein excretion is unquestionably valuable to show gross renal change. Examination of the blood for the abnormal retention of nitrogenous and other elements is of value only in the advanced stages of renal disease.

These laboratory procedures are of value only in supplementing clinical observation. They supply worthwhile information only when conducted with care under controlled conditions, and the results obtained require careful interpretation. Moreover, the tests must be repeated frequently if knowledge is to be attained regarding the progression of the disease process.

Summary and Conclusions. 1. On 12 normal subjects urea and creatinin clearance tests were performed and on 5 subjects dilution concentration tests were carried out. These studies were made to show the normal variations of each test and the effect of changes in one test on the others, and to correlate the results with the physiologic functions of the kidney which they measure.

2. The creatinin clearance test probably gives a close estimate of the absolute degree of glomerular filtration and the urea clearance provides a relative index of this function. Clinically, either test may be used.

3. The ability of the renal tubules to reabsorb fluid is best measured by a concentration test.

4. To attain as adequate an estimate as is possible by laboratory methods regarding the state of renal function, the tests mentioned together with an ordinary examination of the urine will suffice.

5. At best the information gained from these procedures merely supplements that obtained by the actual clinical observation of the patient.

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THE RENAL FUNCTION IN PERSONS WITH ONE KIDNEY.

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THE present study concerns the degree of renal function in 12 patients who had undergone unilateral nephrectomy, in 9 of whom the remaining kidney was presumably normal. Such a study, it was hoped, might give information as to (1) the degree of impairment of renal function occasioned by removal of one kidney, and (2) the extent of reduction in functioning kidney tissue which must occur before such a reduction could be detected by laboratory tests.

Material Studied.—Nine of the 12 patients, 5 men and 4 women, complained of no symptoms and showed no abnormalities of the cardiovascular renal systems. They were from 16 to 50 years of age. None showed albuminuria or abnormality of the urinary sediment. The operative removal of the kidneys was because of pyonephrosis, hydronephrosis, calculus, tumor or trauma. Three of the cases were studied within 2 weeks of the time of operation and again 4 to 5 months later. In 1 of these patients the kidney was almost completely destroyed by hydronephrosis; but in the other 2, 1

of whom had a tumor and the second a congenital anomaly, the renal tissue, although somewhat reduced in amount, was apparently normal in quality and possessed functioning ability. The remaining 5 cases had had nephrectomies performed from 18 months to 6 years previous to the observations.

Of the 3 who suffered from complications 2 had pyonephrosis involving the remaining kidney, and the third had hypertension.

The technique of the renal function procedures carried out is described in the preceding paper.¹ The urea and creatinin clearance values were determined simultaneously. A modification of Volhard's dilution-concentration test was employed, and the excretion of phenolsulphonphthalein 130 minutes after its intramuscular injection was estimated.

Results. The cases have been divided into 5 groups. The division between the 3 groups of longstanding cases without complications is dependent on very slight differences in the results of one or more of the functional tests, but has been made because it facilitates analysis in regard to the physiologic and compensatory changes.

GROUP 1. *Recent Cases.* Tests were performed on Cases 1 and 2 within 2 weeks of operation (Tables 1 and 2). Gross and microscopic examination of the removed kidneys indicated that the renal tissue, although somewhat reduced in extent, possessed functioning ability. In both patients the glomerular filtrates determined by the creatinin method were at the lower limit of normal and the urea clearances were reduced to a parallel extent. In these subjects the maximum concentrating power of the kidneys was possibly slightly diminished. The total fluid excretion was normal and the phenolsulphonphthalein excretion was excellent. In both patients the examinations were repeated 4 to 5 months after the operation. The results obtained were almost identical to those obtained shortly after operation.

GROUP 2. *Cases With Normal Kidney Function.* In 2 cases (3 and 4) the functional tests were normal (Tables 1 and 2). In Case 3 the kidney was removed 20 months previously. The second patient was studied 2 weeks and again 4 months postoperatively, but since the removed kidney was almost entirely destroyed by hydronephrosis, it is reasonable to assume that he had had but one functioning kidney for some time. For this reason it is doubtful how much, if any, of the improvement which is evident from the tests should be ascribed to compensatory hypertrophy of the intact kidney following operation.

GROUP 3. *Cases With Questionable Diminution of Concentrating Ability.* All tests on Cases 5, 6 and 7 were normal except that the patients were unable to concentrate their urine above a specific gravity of 1.020, 1.022 and 1.024 respectively (Tables 1 and 2).

GROUP 4. *Cases With Disturbed Filtration.* Two cases (8 and 9) had glomerular filtrates, as calculated by the creatinin clearance test, below the lower limit of normal, 100 cc. per minute (Tables 1 and 2). In these subjects, however, the urea clearance values and the concentrating power of the kidneys were normal.

TABLE 1.—THE UREA AND CREATININ CLEARANCES, THE BLOOD UREA NITROGEN, AND THE PHENOLSULPHONPHTHALEIN EXCRETION IN 12 PATIENTS WITH ONE KIDNEY.

Patient.	Age.	Arterial blood pressure, mm. Hg.	Duration of nephrectomy.	Diagnosis.	Phthalein excretion, per cent.	Urea.		Blood urea nitrogen, mg. per cent.	Creatinin filtrate, cc. per min.	
						Clearance, cc. per min.	Per cent of normal.			
1	16	118/80	8 days	Congenital anomaly of renal pelvis	70	54	72	8	91	No complications
			5 weeks		..	54	72	..	102	
			5 months		75	52	70	10	98	
2	24	115/80	2 weeks	Tumor	65	44	59	8	81	
			4 months		70	56	75	8	113	
					56	75	86	
3	50	134/84	20 months	Pyonephrosis	45	30*	56	9	132	
					50	50	67	..	75	
4	18	120/80	2 weeks	Hydronephrosis	65	46	75	9	105	
			4 months		45	95	62	13	103	
5	42	108/76	18 months	Trauma	50	92	102	..	163	
					50	71	95	8	180	
6	40	112/70	4 years	Pyonephrosis	45	66	89	10	157	
					65	95	127	..	112	
7	23	114/74	1 year	Calculus	65	72	96	13	113	
					65	66	88	..	105	
8	27	110/68	4 years	Pyonephrosis	35	81	107	5	142	
					75	75	100	15	132	
9	43	120/80	6 years	Calculus	75	53	70	..	125	
					70	65*	121	18	113	
10	47	130/85	12 years	Pyonephrosis	..	122	122	..	65	
					70	96	96	12	76	
11	52	126/76	18 months	Pyonephrosis	20	24	32	14	37	Complications
					20	20	26	15	34	
12	44	230/135	9 years	Pyonephrosis	..	31*	58	..	56	
					..	26*	48	..	57	
						39	52	18	66	
						32	43	..	57	

* Urea clearance expressed in terms of "standard" clearance of Van Slyke. All others are "maximum."

TABLE 2.—THE RESULTS OF THE DILUTION-CONCENTRATION TEST IN THE PATIENTS WITH ONE KIDNEY, SHOWING THE URINE EXCRETION AND THE VARIATION IN SPECIFIC GRAVITY, CONCENTRATION INDEX AND GLOMERULAR FILTRATE.

Subj.	4-hour output, cc.	Day output, cc.	Night output, cc.	Total output, cc.	Specific gravity.		Concentration index.		Filtrate.		Time since operation.	
					Lowest.	Highest.	Lowest.	High'st.	Lowest, cc. per min.	High'st, cc. per min.		
1	1100	1370	235	1605	1.002	1.024	7	164	36	54	5 weeks	No complications
	1220	1485	180	1665	1.001	1.024	5 months	
2	1140	1500	190	1690	1.001	1.021	2 weeks	
	1320	1520	180	1700	1.001	1.023	4 months	
3	1130	1414	355	1770	1.002	1.026	11	210	64	195	20 months	
	1270	1724	541	2265	1.001	1.020	2 weeks	
4	1210	1735	330	2065	1.001	1.025	9	170	78	108	4 months	
	740	1232	520	1750	1.002	1.020	17	178	52	78	18 months	
5	incomplete	190	1.002	1.022	8	189	49	133	4 years	
	812	1133	340	1473	1.001	1.024	8	128	41	112	1 year	
6	507	649	89	735	1.002	1.040	7	265	22	66	4 years	
	1100	1375	310	1685	1.002	1.025	8	120	45	57	6 years	
11	556	incomplete	1.003	1.011	8	55	23	41	18 months	Complications
	734	1194	325	1519	1.003	1.021	8	55	23	41	9 years	

GROUP 5. *Cases With Complications.* The 3 patients (Cases 10, 11 and 12) suffering from complications had had nephrectomies performed previously for pyonephrosis. In 2 of the cases the symptoms and large amounts of pus and albumin in the urine gave evidence that the infection had involved the remaining kidney. In these cases the pathologic process had involved the remaining kidney to an extent sufficient to result in a marked interference with renal function as indicated by the laboratory procedures.

The third patient (Case 12), a man, aged 44 years, on whom a nephrectomy had been performed 9 years previously, had had a known hypertension for 8 years, with gradually increasing cardiac symptoms. All functional tests of his kidneys gave low results. His urine contained much albumin.

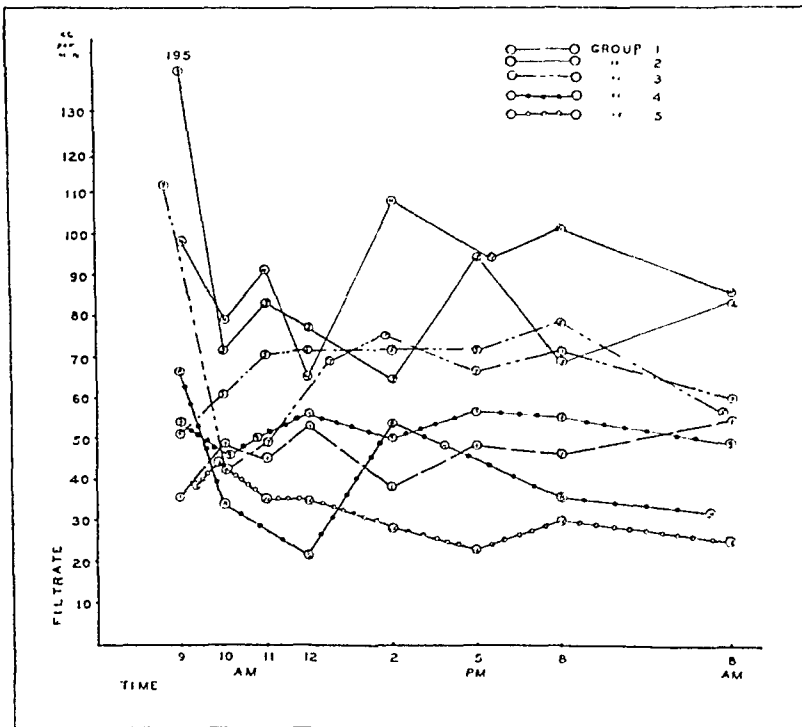


CHART I.—The diurnal variation in glomerular filtrate during a dilution-concentration test in 9 individuals with one kidney.

Daily Variation in the Filtrate. In 9 of the cases the glomerular filtrate was determined throughout a 24-hour period in conjunction with the dilution-concentration tests (Chart I). No creatinin was fed during these examinations. The level of the filtrate determined in this way tended to be lower than that obtained by creatinin clearance tests when the same patients were fed creatinin. The probable cause for this finding, observed also in normal persons, has been discussed previously.¹ The glomerular filtrate remained relatively constant compared to the degree of concentration of the

various urine specimens. Thus in persons with one kidney, as in normal subjects, the diurnal variation in the amount and concentration of the urine excreted is chiefly accomplished by greater or lesser reabsorption in the tubules, and the total amount of glomerular filtrate is altered but little.

Discussion. Experimental work on rats and rabbits with one kidney removed shows that compensatory changes may take place in the remaining kidney.^{2,3,4,5} These changes often consist of an early opening up of a greater proportion than usual of the glomeruli. Later the renal tissue may increase, owing chiefly to an enlargement of the glomeruli and tubules. Whether or not new glomeruli are formed is disputed.

Hinman² has reviewed this subject exhaustively with particular regard to the renal hypertrophy and hyperplasia which may take place in one kidney following damage to the other. Addis, Myers and Oliver⁶ found that in the rabbit the urea clearance values were only about 66 per cent of normal 3 to 4 months after nephrectomy, which corresponded closely to the relative weight of the hypertrophied remaining kidney. In dogs, following nephrectomy, there is an immediate depression of function, but the urea excretion is normal in about 11 days.² Foster⁷ studied 9 patients within 3 weeks after nephrectomy and found the phenolsulphonphthalein excretion normal and the kidney's concentrating ability little if any impaired. In these patients the Addis urea test showed values ranging from 19 to 36, whereas 50.4 is the theoretical normal. Seven of the 9 patients were suffering from renal tuberculosis.

Our results show that following unilateral nephrectomy there may or may not be detectable impairment of renal function.

Immediately following the removal of the kidney the renal reserve in the remaining one is brought into play. In our Cases 1 and 2 it is probable that the increase in function was accomplished partly by greater filtration through the individual glomeruli. Since the tubular reabsorption of fluid was diminished, as indicated by the concentration tests, and since there was no evidence of damage to the tubular cells which could explain this decreased reabsorption, it is probable that it was due to an increased volume of filtrate flowing down each tubule.

The examinations in Cases 1 and 2 carried out 4 to 5 months postoperatively showed no change in function, suggesting that in these particular cases there was little or no actual structural hypertrophy of renal tissue within this period of time. However, subsequent to unilateral kidney removal certain compensatory changes may conceivably take place. Groups 2, 3 and 4 illustrate these changes.

1. There may be functional or structural compensatory changes in both glomeruli and tubules producing a normal renal function. Cases 3 and 4 may be of this type.

2. There may be compensatory changes in the glomeruli, but the tubular compensation is relatively less. Consequently, the total glomerular filtrate is normal in amount but the reabsorbing ability of the tubules is inadequate to provide maximal concentration (Cases 5, 6 and 7).

3. The glomeruli may not undergo compensatory changes and the glomerular filtrate may remain diminished below normal. Under these conditions the tubules can reabsorb water to a high degree and, moreover, they are apparently able to readjust themselves qualitatively so that less urea than normal diffuses back through their walls into the blood. Therefore, although the values found for the creatinin clearance (*i. e.*, filtrate) are somewhat low, the urea clearance values are normal. Cases 8 and 9 belong in this group.

This study also furnishes some information as to the sensitivity of the functional tests employed. In Cases 1 and 2 approximately 30 per cent of the total amount of functioning kidney tissue had been recently removed at operation. Both the creatinin and urea clearance tests showed a reduction of this order of magnitude from the average normal. It would seem not improbable, therefore, that the creatinin clearance test actually gives an absolute and the urea clearance a relative index of glomerular filtration. The values obtained by the urea clearance procedure, however, may be influenced by changes, compensatory or otherwise, which may occur in the tubules. This, however, does not impair the clinical value of the test.

The concentration test does not measure the total amount of functioning tubular tissue, but rather the conditions under which the individual tubules operate. That is, on the one hand, if the quantity or velocity of fluid passing down a normal tubule is increased, it will be unable to concentrate to the usual degree; on the other hand, if the actual tubular structure is altered by disease, an individual tubule may prove incapable of concentrating a normal or even diminished amount of glomerular filtrate. Therefore, an accurate evaluation of the nature of any disturbance in tubular function detected by a concentration test, can be properly attained only by correlation with an estimate of the amount of glomerular filtration.

This study indicates that the renal function of persons with one kidney is completely adequate for their daily needs. The only hazard to such individuals is in the development of complicating disease in the remaining kidney.

Summary and Conclusions. 1. The renal function of 12 patients who had undergone unilateral nephrectomy was studied by urea and creatinin clearance, concentration and phenolsulphonphthalein tests. Nine of the patients were quite healthy, 2 had pyonephrosis of the remaining kidney and 1 had hypertension.

2. The 2 cases which were studied immediately after operation

showed diminished values for the clearance and concentration tests. The tests on 7 other uncomplicated cases were normal in 2, and one or more of the tests were slightly abnormal in 5. The 3 patients with complications had marked impairment of renal function.

3. In the absence of complications, the renal function of persons with one kidney is not only adequate, but possesses a reserve capacity as well.

4. The observations confirm the value of urea and creatinin clearance tests in detecting early and quantitative reductions in glomerular function and of the concentration test as a measure of tubular reabsorptive power.

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NOTES ON THE NATURE OF THE SPLENIC CHARACTERS IN BANTI'S SPLENOHEPATIC ANEMIA AND A METHOD FOR SCORING THEM.

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THE following notes will attempt to assist in the verbal delineation of the spleen in the conditions known as Banti's disease and splenic anemia. The work is a part of the studies attempting to give score values to the diseases of this organ, these notes being particularly devoted to the study of a special group.

The evaluation of changes in the spleen, a sort of scoring system, grew from a request by a surgeon to give figures comparable to those in the method used in the tabulation of tumors, while the part concerning the splenic anemias grew from a remark by an internist that the pathologist could not help in a clinical diagnosis by examination of an excised spleen. Attempts at scoring have met with the difficulty that was foreseen, that of giving a numerical value to a qualitative change. The difficulty of distinguishing between the splenic anemias on the basis of splenic pathology is that there is no clear definition of the clinical terms "splenic anemia" and "Banti's disease."

Studies of this subject fall into the following headings: (1) A description of the tissues from presumably normal and from pathologic organs and the numerical evaluations to be put upon them; this is the basis of a scoring system. (2) The identity of the clinico-pathologic states called splenic anemia and Banti's disease. (3) The character of the spleen in the two. (4) The distinctions, if any.

Technique of Scoring. The scoring of the spleens was started by preparing a chart to cover every possible alteration in the gross and microscopic anatomy of the organ. This has suffered many modifications and reductions, until finally it was decided that scoring of the gross anatomy was not at all profitable. Numerical evaluation has not led to a final scheme of scoring in figures approaching in definiteness that used for epidermoid carcinoma, which in itself is useful in only a broad and relative manner and by those familiar with it. None the less, a helpful scheme for the micro-anatomy was produced by reducing to the minimum the characters (Table 1) that had to be evaluated, which were found to be 13 in all. Their nature is discussed in the following paragraphs as a basis for these descriptions and enumerations.

TABLE 1.—EXAMPLES OF THE SCORING OF SPLEENS ACCORDING TO THE ARBITRARY MATHEMATICAL SYSTEM AND THE OBSERVATIONS JUST MADE.

	Theoretically normal.	Actual reading normal age 19.	Actual reading normal age 22.	Reading of most complete case of proven Banti's disease.	Reading of almost typical case of splenic anemia, clinically. Traces of case lost.	Score of purpura hemorrhagica.
Follicles	2	2	3	1	3	3
Germ centers	2	1	1	1	2	3
Pulp	2	2	2	1	1	2
Sinuses	2	2	3	3	3	3
Sinus endothelium	2	2	2	3	2	2
Bloodvessels	2	2	2	3	2	2
Bloodvessel wall disease	2	2	3	3	2	2
Fibrous tissue	2	2	2	3	2	2
Reticulo-endothelial cells	2	1	2	3	2	3
Blood	2	2	2	1	3	2
Pigment	2	2	1	3	2	2
Neutrophils	2	2	2	3	2	2
Eosinophils	2	2	2	2	1	1
Total	26	24	27	30	27	29

Two organs of presumably normal character were fortunately obtained, one from an executed man and one from an accidental death; the men were 22 and 19 years of age, respectively. The characters were given a numerical normal value of 2. If they were reduced in number, smaller in size, they were estimated as 1, whereas, if they were increased, hypertrophic or hyperplastic, they were scored as 3. Allowance in a side chart was made for adventitious changes such as the appearance of myeloid cells, amyloid, abscess, tumors, tubercles and infarcts. These were not scored because they would not be present in any normal spleen.

Follicles. The normal follicle is assumed to be a fairly solid collection of lymphoid cells either as a true Malpighian body or as a periarterial spindle. In youth up to 10 years there may be a recognizable "germ center" in a large percentage of follicles. After youth they become progressively fewer and one or two per ordinary section would be within normal limits; if there were none at all they would be registered as reduced.

The normal *follicles* vary from 60 to 100 per sq. cm. of the average microscopic specimen taken just within the subcapsular area. The measurement of their width is so variable that it cannot be quoted even within wide limits. The number of the follicles in enlarged spleens is usually reduced. In none of the spleens of any kind in all this study has there been any evidence of an increase in the number. The number of follicles per sq. cm. in cases diagnosed as Banti's disease has ranged from 9 to 33. The gross bulk of these spleens has been from 2 to $2\frac{1}{2}$ times the bulk of normal spleens. The bulk of the spleen has been determined by the amount of water displaced. It would, therefore, appear that the reduction of follicles is not due to their disappearance but to their inactivity and their compression by the increased interlying organic mass. Two of the spleens, coming from cases not diagnosed as Banti's disease, had, respectively, 34 and 47 follicles per sq. cm. of a pathologic section and their organic bulk was about twice the normal bulk; the bulk of these two organs was less than that of the spleens from cases satisfactorily diagnosed as Banti's disease. It would appear that those cases that are probably different from the acceptable Banti anemia may have less reduction in the number of follicles as well as less atrophy of the individuals.

The small *splenic lymphocytes* are usually arranged in cords but this systematic and conventional construction is not traceable in all pathologic spleens. These cells must be judged by their apparent abundance or paucity in a given specimen by comparison with an acceptably normal one. In the hemorrhagic purpuras, sometimes in the primary anemias, and in most of the infectious processes, there is an abundance of splenic cells with considerable cytoplasm and a relatively loose nucleus that are to be considered as young or swollen small lymphocytes. Cells corresponding to the youngest or lymphoblast type are only recognizable by special cytologic techniques. Hyperplasia of these elements is to be looked for only in leukemias and some infectious diseases.

Sinuses. Under normal conditions the sinuses are usually traceable but are best seen in early hyperemia, both active and passive. One must know in judging a given spleen if it has been incised or perfused. The sinus reticulum is detectable with difficulty and for its demonstration the organ cannot be pressed but should be fixed with the greatest care, whereupon special stains by the silver methods will reveal the delicate filamentous tracery. It is practically absent in chronic splenomegaly, fibrosis beside the sinus overshadowing it in density. Sinus endothelium is flat and obscure in the normal organs but it is prominent in all chronic conditions and in the majority of acute ones also. In the chronic cases it often seems heaped up. The cells comparable to it seem to occur in groups beside the sinuses and sometimes beside the trabeculae. On one occasion a perfect mantle of endothelium was seen around an arteriole, the arrangement suggesting that of endothelioma; this was not in a case of tumor or Gaucher's disease but in a hemolytic anemia. In the early cases of the Banti type there is a moderate prominence of these cells but in the late cases they are not conspicuous.

Bloodvessels and their walls in the normal spleen are not particularly prominent but show considerable variation in different parts of the same organ. They should only be readily discernible near trabeculae and in follicles. The walls of vessels are, after adolescence, frequently abnormal;

about one-fifth of the vessels in the two supposedly normal spleens studied showed hyalin change of the media, occasional swelling of the endothelium and unusually wide adventitia.

Fibrous tissue in the normal spleen is best understood by the use of a stain like phosphotungstic acid-hematoxylin, the special ones like silver impregnation giving too great a contrast and prominence to the supporting framework. By a good stain it is evident that the fibers are coarser and more numerous than has been usually described. There are two places in which the normal supporting tissue is best examined—around the follicles and just outside the sinuses.

The lower degrees of fibrous tissue increase are difficult to decide upon; more advanced grades are relatively easy. Apparent or relative decrease in fibrous tissue is perceptible in the acute "splenic tumors" such as occur in septicemia and typhoid and in the chronic swellings of the purpuric and hemolytic types. It is in both instances almost certainly relative, there being no reason to assume that true destruction occurs.

Reticulo-endothelial cells are usually plainly visible in the two forms that may be recognized for the spleen—the large mononuclear lying in a lacuna of the pulp and the medium sized mononuclear lying between the sinuses and lymphoid groups. Their increase is perceptible, and largely confined to the medium sized mononuclears, there being increase of giant mononuclears only in the lipoidic spleens. A decrease in the mononuclears is probably relative and only to be expected when their place is taken by blood, fibrous tissue and lymphocytes. Sometimes these cells are distinctly phagocytic, but in the absence of marked pigmentation, phagocytosis is not a prominent feature of splenic pathology; the malarial and hemolytic anemias are exceptions.

The presence of *blood* within vessels and sinuses and diffusely within the splenic tissue is readily perceived, but its amount depends upon the method of the removal of the spleen and its treatment afterward. In the more acute cases of the hepatosplenic anemias the blood is found uncoagulated and agglutinated; in some of the later cases both of these features may be found.

Pigment under normal conditions is sparse in the spleen and yet, in the two probably normal spleens studied, several small groups were found lying free and one large group was found in a giant mononuclear.

Neutrophils scattered singly throughout the tissue are much more common than is generally supposed; this is also true of the eosinophils. Under conditions of acute infection, hemolytic anemias, Hodgkin's disease, tuberculosis and the like, both of these types may be found increased. In 18 cases of the Banti type that we have examined especially for this cell, they have exceeded normal 4 times. Eosinophils are, however, definitely less readily found than are the neutrophils, but occasionally they may be quite prominent. They seem to be more common in the younger cases than in the older ones of chronic splenomegaly, and are very conspicuous on account of their redness.

Splenic anemia may be defined, according to the writings of Osler (1902), Stengel (1904) and Rolleston (1914), as a chronic anemia with splenomegaly (which is often the first change), of unknown cause, with a blood picture with a low color index, a reduction of red cells possibly hemolytic in origin, leukopenia or normal white count, moderate reduction of thrombocytes, no lymph gland enlargement, liability to gastro-intestinal hemorrhages and with an illness naively stated by Rolleston as "prolonged with a tendency to spontaneous cure and with splenectomy curative, if successful."

Banti's disease is like this, but passes into a stage in which cirrhosis of the liver is the prominent pathologic feature and which is combined with jaundice, ascites, further anemia and fatal end. According to Rolleston, Banti's disease occurs more in females and below full middle age; he suggests that the reverse is true in splenic anemia.

Briefly then, the distinction from a clinical standpoint is that in splenic anemia there is no hepatic disease, whereas when cirrhosis and ascites appear it should be called Banti's disease. MacCarty in his analysis states, "For practical purposes the two diseases are usually considered as one."

It might be profitable to devote a few lines to indicate how these words came into use and make mention of a recent discussion on the subject. Stengel credits the origin of the term splenic anemia to W. Griesinger in the middle of the 19th century, but adds that Banti emphasized the term in 1884. Banti himself states that Gretzel (a pupil of Griesinger) in 1866 first made use of the name.

The Italian author described a disease of three stages, insidious and of long duration, many years indeed, consisting of anemia and enlarged spleen, a quiescent period of variable length and a terminal stage of hepatic cirrhosis and ascites. He recognized the similarity of this disease and splenic anemia but insisted that they were different because of the duration, course and hepatic change. Senator, 1901, noted that to the symptom complex described by Banti, gastro-intestinal hemorrhages and local escape of blood might be added. He thought that hepatic cirrhosis need not cause the ascites which could be due to venous obstruction by the large spleen.

Disease of the walls of the splenic artery and vein have been mentioned several times in the literature and thought to be the cause of the splenohepatic disease. Certain other diseases, such as Gaucher's disease and tuberculosis of the spleen, were formerly confused with the conditions under discussion.

Rolleston, commenting on these diseases, makes the point that the stages need not be so protracted as Banti would have it and may indeed so run together that no sharp limits can be detected. He states that there are certainly cases corresponding to the description of Banti but that they appear to be more in the ward than on the autopsy table.

At the meeting of the Association of American Physicians, May, 1932, a discussion took place under the stimulation of a report by Howard and Mills, whose work credited the existence of a clinicopathologic state that corresponds to Banti's disease, yet over half of their cases failed to show hepatic changes. Dr. Howard thinks that only a limited number of cases should rightly be called Banti's disease, but that such undoubtedly exist.

Possibly some of the following considerations will help to decide whether these two terms are justifiable. The condition has not much improved since the very pertinent words of Stengel, 1904,

when he states: "It would be hopeless in the present state of knowledge to attempt a classification of all of the cases that have been reported. On the other hand, it is very evident that there are very different sorts of cases that have more or less superficial resemblance, and I cannot share the view that all are probably instances of one disease in different stages."

Judging from 13 fresh spleens that have been examined grossly and in which clinical diagnoses were acceptable, the features were so nearly constant without regard to diagnosis that they may be described together. Whether or not there are several diseases represented, the gross appearance of the organ does not help to solve the matter. To these have been added the records of 10 other cases and all 23 have been studied microscopically.

The Spleen. It weighs from 600 to 1600 gm. The general shape is preserved, the notch being usually perceptible. The general splenic outline falls within normal variations; the capsule is slightly thickened, smooth, regular, translucent. There may be patches of local chronic perisplenitis, which are best ascribed to reaction to local trauma or to inflammation in the vicinity; there is no reason to believe that perisplenitis would arise from endosplenitis. The cross section is usually dark brown, firm, rather homogeneous in appearance with a perceptible increase in delicate red-gray strands that correspond to a multiplicity of fine trabeculae. Faint red-gray dots may suggest the Malpighian bodies but a prominence of such markings has not been recorded.

It has been one of the outstanding pathologic and etiologic features of the pathologic anatomy of the spleen and liver in these conditions to emphasize the existence or possibility of sclerosis of the splenic vein and of the gastro-splenic artery. In 1 case, of the series here discussed, there were found endophlebitis and obliterative endarteritis between the liver and spleen, and in 1 case a sclerosing and calcifying phlebitis. The condition of the splenic vein should be noted with greater exactness by both surgeons and pathologists.

The microanatomy of the spleen in the cases of the present study is now taken up in order of the features that we have found important.

The capsule is slightly thickened, and beneath it there is no loose space that could pass for a marginal sinus, the pulp tissue growing up directly to the fibrous coat.

The follicles are diminished in number and size. The "germ centers" are for the most part somewhat below normal limits of size and number, although there are many instances in which they may be plainly seen. Where they are seen there is a hyalin change in the interstitial fibers, or the entire central zone of the follicle may be a hyalin mass with a cell or two and usually without recognizable bloodvessels. This hyalin mass may at times contain many silver-staining fibrils.

It has already been emphasized that the number and size of the follicles should be estimated in terms of the size of the whole spleen. This relative value assists very materially in estimating their increase or decrease—an item again mentioned in discussing two spleens that vary in microscopy from the Banti picture.

The pulp is usually poor in small lymphocytes and, with rare exceptions, never contains what would be called an excess thereof.

The sinuses are for the most part dilated. The sinus endothelium is usually inconspicuous. It may seem atrophic and there is rarely, if ever, a desquamation of endotheliocytes. Care must be taken in interpreting this, because in many studies spleens are perfused while many others are opened and allowed to drain and collapse. When the organ is removed by operation the hemostats or clamps should be allowed to remain on the vessels of the stalk until the pathologist has opportunity to perfuse the spleen or cut it immediately before it is put into fixative. About one-third of our specimens were perfused. The irregularity of the chance to carry out this technique has made it almost an impossibility to compare organs removed during early stages *versus* those from cases of longer duration.

The bloodvessels are within normal limits of number. The arterioles of follicular centers, of the edge of trabeculae and the occasional one in the pulp, show slightly more disease in the wall than they would in a presumably normal spleen of comparable age; this is true irrespective of the duration of the disease.

The veins of trabeculae are usually distended. There is often a hydropic change in the media and on two occasions there were early calcium deposits. Marked pathologic change in these veins is, however, not an outstanding feature.

Fibrous tissue is everywhere increased. In the cases in which the spleen has been removed less than 1 year from the inception of symptoms, the fibrous tissue increase is almost as easily recognized as in cases existing much longer than this. Occasionally a deeply stained band, shown by Van Gieson or silver methods, may completely surround a follicle. The perivascular fibers are prominent. The trabeculae seem to spread out as numerous delicate, yet intricately wound and mixed silver-staining fibers; some of the strands running through the pulp may be massed and hyalin.

Reticulo-endothelial cells appear to take the usual two forms. The large single mononuclear giant cell is not increased; the moderate sized mononuclear, resembling an endotheliocyte, is definitely increased. The endotheliocyte is plainest in spleens that have been removed about 1 year after inception. They lie along the sinuses, sometimes in veins and occasionally in a row along the connective tissue strands. It does not seem possible that their number contributes very greatly to the increased size of the organ.

The amount of blood in the organ, as judged by the microscopic

appearance, is quite variable. It gives a slightly lower score value in spleens removed within 3 full years since the first symptom, and more in organs removed in later years. This observation is not in accord with those on specimens studied by the writer some years ago, coming from supposed Banti's disease of less than a year's duration, that were found to contain much more blood, while another case of long standing was quite poor in free blood. Aschoff and McCallum think that the earlier stage is accompanied by excessive bloodiness. However, not all cases progress at the same rate, and not all spleens have been handled for examination in the same manner.

Pigment is slightly increased and varies directly with the amount of blood perceptible in the sections.

Neutrophils, eosinophils and plasma cells appear to be of no significance. Other recognizable marrow elements are not recorded.

There are 2 cases in the 23 specimens in which the follicles stand out as different from the others and in several ways there are slight variations from the picture just given. These 2 cases deserve a little attention.

The follicles in these cases were all larger than the average of the 2 presumably normal organs and of 34 routine spleens from autopsy material. In these 2 the "germ centers" were apparently more prominent. In both cases the bloodvessels were more numerous. The reticulo-endothelial cells were less conspicuous, the blood within normal limits, the pigment perhaps slightly increased. These cases, respectively 4 and 22 years old, both had their spleens removed after at least 1 year of illness (one 5, the other unknown). The distinction of these two spleens from the others is more readily apparent to the eye than from the written description. They have been diagnosed as splenic anemia, an apparently justifiable distinction in at least one of them, since there was neither jaundice nor ascites, and 3 years have passed after splenectomy without the appearance of ascites.

The liver in the 23 cases has been changed clinically in 10 of 16 instances where it is mentioned, and actually changed, as seen at operation or autopsy, in 7 out of 14 in which it is mentioned. Jaundice was present in 3 out of 14 cases, of which the history records dependable observations. Ascites was present in 6 out of 20 cases and corresponded with definitely known change of the liver 4 times out of the 6. Of the 23 cases, 6 died following splenectomy, 8 are reported living 3 to 8 years and all are invalided. Six of these 8 are recorded as having had postoperation hemorrhages.

Discussion. A distinction of the types of spleens and a clear separation of all these cases into splenic anemia on one hand and Banti's disease on the other seems at present very difficult. The clinical evidence at hand supports strongly the thought that there is a probability of liver damage in most cases of chronic spleno-

megaly. Only 2 of 14 traceable cases seem to have passed 2 years without clinical or definite pathologic information that the liver was involved. The evidence would support the idea that there is a condition of Banti's disease, the early stages of which are splenomegaly with anemia. The late stages are chiefly hepatic with jaundice and ascites. The name Banti's splenohepatic anemia is suggested. Those that do not fall into this group, ably covered by Stengel,⁴ remain yet to be classified and the term splenic anemia would better be restricted to description and discussion.

The spleen of Banti's splenohepatic anemia can be described as an enlarged organ, without characteristic capsular change, with reduction in the size and relative number of follicles, fibrosis of follicular centers, of pulp and of trabecular lines, a prominence of mononuclears, a relative atrophy of the pulp, and a variation of blood and pigment depending upon the duration of the enlargement. It is distinct from the enlargement due to primary hepatic cirrhosis which has marked congestion, pigmentation, prominence of lymphoid structures and limited fibrosis. It is distinct from the hemorrhagic purpuras and anemias which have much blood and pigment, a prominence of endothelial cells and phagocytes, and a relative paucity of silver-staining fibers. It is distinct from malarial spleens because the latter show pigmentation, a fine fibrosis, diffuse lymphoid hyperplasia with much phagocytosis. It differs from the syphilitic and tuberculous spleens by the absence of distinct inflammatory foci. With these one finds a combination of marked sinus catarrh, plasma cells and eosinophils; masses of endotheliocytes may be present in these spleens. It is separated from Hodgkin's disease of the acute type by the presence in the latter of large zones of endotheliocytes, giant cells, eosinophils and polymorphonuclears, and from the chronic type with less ease because of the irregular fibrosis of this form.

It would seem from this survey that a strict scoring of the splenic characters will not lead to a numerical value that can be definitely identified with these specific clinical or pathologic entities. By familiarity with this method, or one like it, it may be possible to obtain distinct leads as to the part of the organ that is giving the most definite reaction.

The characters discovered do not permit a sharp separation of the spleens that come from cases called Banti's disease and those called splenic anemia. Many chronic splenic anemias are associated with hepatic disease comparable to that described by Banti. The clinical terms are not used with critical care. It cannot be stated that any considerable number of the cases with splenomegaly and anemia, in which splenectomy was done, may not have terminated with hepatic disease. These studies include one complete record of Banti's disease diagnosed before splenectomy, when there was nothing to suggest hepatic disease by observation at laparotomy,

that died from pneumonia 2 years later and showed a cirrhosis and ascites.

Therefore, it seems acceptable to use the term "splenohepatic anemia" or "Banti's disease" and to omit the clinical diagnosis of splenic anemia, employing instead "anemia with splenomegaly." There may be cases in the melange of the obscure anemias that have simply enlargement of the spleen, anemia and gastro-intestinal congestion that will not go on to hepatic pathology. They are probably rare and further study may identify them.

The characters of the spleen in Banti's disease will help to make the clinical diagnosis and are to be summed up as diminution in the size and relative number of follicles per square area; an increase of fibrosis around follicles, along sinuses and in the neighborhood of trabeculae, and a prominence of many fine trabeculae; a hyalin accumulation in the center of follicles, a prominence but no great exaggeration of large mononuclears, and a slight increase of pigment.

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DETERMINATION OF NON-PATERNITY BY MEANS OF BLOOD GROUPS.

WITH SPECIAL REFERENCE TO THE AGGLUTINOGENS M AND N OF LANDSTEINER AND LEVINE.

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IN our country the possible application of blood grouping in medicolegal cases for the determination of non-paternity has not received the recognition that it has received in many European countries. So reliable is the application of blood grouping for this purpose, that in 1929 Schiff¹ succeeded in collecting 5584 cases in which blood groups had been so applied in Germany, Austria, Denmark, Sweden and Switzerland. Since 1929 this method has also been adopted in Russia, Norway, Japan, the Netherlands, Italy, and Great Britain.

That human bloods can be subdivided into definite groups, because of the ability of the serum of one normal individual to agglutinate the red blood cells of certain other human beings, was first recognized by Landsteiner in 1900.² Landsteiner explained this phenomenon by postulating the existence of two isoagglutinogens, A and B, in the red blood cells, and of two isoagglutinins, α and β , in the blood serum, such that α is specific for A, and β is specific for B.³ In Table 1 is shown the difference in composition of the 4 Landsteiner blood groups, together with the old numberings of Moss and Jansky, and the international nomenclature officially recognized by the Health Committee of the League of Nations. The old nomenclatures, no longer used in scientific publications, are only given here because they are still being used in some of our hospitals. The existence of two systems of numbering has resulted in confusion on many occasions, and has also been responsible for several transfusion accidents. Since the international nomenclature depends upon the agglutinin content of the red blood cells, it can cause no confusion.

TABLE 1.—CLASSIFICATION AND COMPOSITION OF THE LANDSTEINER BLOOD GROUPS.

Jansky.	Moss	International.	Cells (agglutininogen).	Serum (agglutinin).
I	IV	O	—	α and β
II	II	A	A	β
III	III	B	B	α
IV	I	AB	A and B	—

In 1908, Epstein and Ottenberg presented the first data on the heredity of blood groups.⁴ In 1910, von Dungern and Hirschfeld⁵ showed that the agglutinogens A and B are inherited as Mendelian dominants; and in 1924, Bernstein⁶ demonstrated that the heredity of the agglutinogens A and B depends upon three allelomorphous genes, A, B and R, where A and B are dominant, and R is recessive. Therefore, the 4 blood groups may be subdivided into genotypes as follows: Group O, genotype RR; Group A, genotypes AA and AR; Group B, genotypes BB and BR; and Group AB, genotype AB. The heredity of the Landsteiner blood groups, according to the Bernstein theory, is shown in Table 2.

TABLE 2.—HEREDITY OF THE LANDSTEINER BLOOD GROUPS.

Groups of parents.	Groups of children possible	Groups of children not possible.
O \times O	O	A, B, AB
O \times A	O, A	B, AB
O \times B	O, B	A, AB
A \times A	O, A	B, AB
A \times B	O, A, B, AB	
B \times B	O, B	A, AB
O \times AB	A, B	O, AB
A \times AB	A, B, AB	O
B \times AB	A, B, AB	O
AB \times AB	A, B, AB	O

How the blood groups can be applied in an actual paternity case is illustrated in the following two hypothetical examples: A man charged with the paternity of a child denies ever having had intercourse with the plaintiff, so the blood groups of man, woman and child are determined. The man is found to belong to Group A, the woman to Group A, and the child to Group B (see mating 4 of Table 2). Since the mother does not possess agglutinin B, but the child does, this agglutinin must have come from the father, who could therefore only belong to Group B or Group AB. The blood groups in this case, therefore, have furnished absolute proof of the man's innocence. Let us suppose, on the other hand, that in another similar case the blood groups were as follows: man, Group B; woman, Group A; and child, Group AB. As may be seen from Table 2 (see mating 5), such a combination of groups is entirely possible. This, however, is no proof that the man charged with paternity is the true father; for in a population such as that present in this country, about 15 per cent of all individuals belong to Group B. The man in question is no more proved to be the father than is any other man belonging to the same group. Blood groups, therefore, are of no value as an aid to proving paternity; they can only be used to prove non-paternity.

In not every case where a man is unjustly accused of paternity is it possible to exclude him as a father of the child. Thus, if the putative father and the true father both belong to the same group, no exclusion will be possible. It has been calculated that the average chances of proving non-paternity by means of the Landsteiner blood groups are approximately 1 in 6.^{7,8}

The chances of proving non-paternity have been doubled by the discovery by Landsteiner and Levine of several additional agglutinogens in human red blood cells.⁹ Two of these, termed M and N, respectively, were studied in great detail, and Landsteiner and Levine demonstrated that they are inherited as Mendelian dominants.¹⁰ According to their theory, the heredity of these agglutinogens depends upon a single pair of allelomorphic genes, M and N. There are therefore only three genotypes possible: MM, MN, and NN; corresponding to the three phenotypes: M+N- (blood possessing agglutinin M, but lacking agglutinin N), M+N+ (blood possessing both agglutinogens, M and N), and M-N+ (blood possessing only agglutinin N). According to the theory, therefore, bloods of type M-N- (lacking both agglutinogens) are impossible. As a matter of fact, although almost 20,000 specimens of blood have been examined to date by Landsteiner and Levine, Schiff,^{11,12} Wiener, *et al.*,^{13,14,15} Thomsen,¹⁶ and Clausen,¹⁷ not a single blood lacking both agglutinogens has been found to date. The present author has personally examined more than 3000 specimens of blood without finding a single exception to this law. This, certainly, is impressive confirmatory evidence of the theory of Landsteiner and Levine.

The heredity of the agglutinogens M and N is very easily derived from the theory, as shown in Tables 3 and 4. Thus, in the $M+N- \times M+N-$ mating, the genotype of both parents is MM. The gametes (sperm and ova) each contain the single gene M, so that all the zygotes must be of genotype MM. All the children of such a mating must therefore be of type $M+N-$. Similarly, in the $M+N- \times M+N+$ mating, the genotypes of the parents are MM and MN, respectively. The former parent can only produce gametes containing gene M, the latter parent produces gametes with gene M and gametes with gene N in equal numbers. Half of the zygotes must therefore be of genotype MM and half of genotype MN, corresponding to the phenotypes $M+N-$ and $M+N+$, respectively. The other four matings in Table 3 were worked out in a similar manner.

TABLE 3.—HEREDITY OF AGGLUTINOGENS M AND N.

Cross.	Percent children of types.		
	$M+N+$	$M+N-$	$M-N+$
$M+N+ \times M+N+$	50	25	25
$M+N+ \times M-N+$	50	0	50
$M+N+ \times M+N-$	50	50	0
$M+N- \times M-N+$	100	0	0
$M+N- \times M+N-$	0	100	0
$M-N+ \times M-N+$	0	0	100

TABLE 4.—MEDICOLEGAL APPLICATION OF THE AGGLUTINOGENS M AND N.

Types of parents.	Types of children possible.	Types of children not possible.
$M+N+ \times M+N+$	$M+N+$, $M+N-$, $M-N+$	
$M+N+ \times M-N+$	$M+N+$, $M-N+$	$M+N-$
$M+N+ \times M+N-$	$M+N+$, $M+N-$	$M-N+$
$M+N- \times M-N+$	$M+N+$	$M+N-$, $M-N+$
$M+N- \times M+N-$	$M+N-$	$M+N+$, $M-N+$
$M-N+ \times M-N+$	$M-N+$	$M+N+$, $M+N-$

Technique. The technique of testing for the agglutinogens M and N is much more complicated than the technique of testing for A and B. There are no natural agglutinins for M and N; the testing sera are obtained by immunizing rabbits. To produce anti-M serum, blood of type $M+N-$ should be used; to produce anti-N serum, blood of type $M-N+$ is used. The blood selected should also belong to Group O, so that no agglutinins are formed against A and B. The technique I have found most effective is to alternate courses of daily intravenous injections with long rest periods. If 12 rabbits are to be immunized, 25 cc. of blood will suffice for one course. The blood should be divided among 7 or more tubes (for a course of 7 days or longer), containing the following solutions, recommended by Rous and Turner¹⁸ for preserving blood: 5.4 per cent glucose (5 parts); 3.8 per cent sodium citrate (2 parts); whole blood (3 parts).

The solutions must be sterile, and the blood must be collected under sterile precautions. When stored in the ice box in this manner, blood may be kept for several weeks. Before injecting the blood into the rabbits, the contents of each tube should be washed with sterile saline and then diluted up to a convenient volume. The washed blood is then divided equally among the 12 rabbits. All the injections of the first course are given intravenously. The first injection of each of the subsequent courses is given

intraperitoneally (to avoid anaphylaxis); all other injections are given intravenously. The rest periods between courses should be about 7 to 10 days. The rabbits are bled and the sera examined for their agglutinin content 1 week after the last injection. After 3 or 4 courses of injections, most rabbits will produce good anti-N sera. It is much more difficult to produce anti-M sera, however. We finally succeeded in producing a very potent anti-M serum, by giving 2 rabbits which had had several courses of injections, followed by a rest period of *several months*, 1 additional course of injections. When preparing these sera it is wise to start with a large series of rabbits, since because of the protracted nature of the immunization (particularly for M), most of the rabbits will die before the experiment is completed.

To test the sera a few cubic centimeters of blood are collected from an ear vein and then allowed to clot. The serum is separated off by centrifuging, and then inactivated by heating to 56° C. for half an hour. This serum not only contains agglutinins against M (if the rabbit was immunized with M+N- blood) or N (if the rabbit was immunized with M-N+ blood), but also species agglutinins acting on all human blood. A potent serum will agglutinate any human blood at a titer of 1 to 3000. To prepare the testing fluid from the serum, the species agglutinin must be removed by absorption. We prepared our anti-M fluid from serum M 905. This serum was diluted 50 times and mixed with half a volume of packed, washed cells of type M-N+. After standing for 30 minutes at room temperature, the mixture was centrifuged at high speed. The supernatant fluid now only contained agglutinins against the factor M. Our N fluid was prepared from the serum of rabbit N 2. This serum was diluted 20 times and absorbed with half volume of packed, washed cells of type M+N- at 37° C. The testing fluids thus prepared were stored in the ice box after the addition of 1 drop of toluol per cubic centimeter of fluid. (The use of this preservative was suggested to us by Dr. Philip Levine. The addition of toluol preserves the testing fluid for more than 6 months. Without toluol, on the other hand, the testing fluid deteriorates rapidly and usually must be discarded after a few weeks.) Before use, the M fluid was further diluted three times (making a final dilution of 1 to 150), and the N fluid two times (a final dilution of 1 to 40).

The blood to be tested is suspended in saline and citrate, washed once and resuspended in normal saline solution to make a 2.5 per cent suspension. One drop of the cell suspension, 2 drops of saline, and 1 drop of testing fluid are mixed in a small test tube, the mixture is then centrifuged for 5 minutes at 1800 r.p.m. After centrifuging, the tubes are replaced in the rack, which is then shaken until the negative control has broken up into an even suspension. (Control bloods of all three types must be included in every experiment.) The reactions for M are always easy to read. There will be occasional difficulty with the N reactions, however, but whenever this occurs the difficulty will resolve itself if several different N fluids are used, and if the tests are repeated a sufficient number of times.

We did not find it necessary to use any preservative for the concentrated immune rabbit serum. After the preliminary tests had been performed, the rabbits which had been found to have potent sera were bled from their marginal ear vein, which was cut after the ear had been previously rubbed with a small amount of xylol. In this manner, as much as 40 cc. of blood could be obtained, and at the same time the rabbit could be kept alive for further experimentation. The blood was allowed to drip into sterile 10 cc. tubes, and after the blood had stood overnight in the ice box the serum was separated by centrifugation. The serum was then transferred to sterile 1 cc. vials by means of sterile pipettes. The vials were hermetically sealed, and the serum was then stored in the ice box. Serum so kept was

found to show no appreciable diminution in titer after two years, provided that there was no contamination. The serum that is to be stored need not be inactivated, since it loses its complement after standing for several days in the ice box.

Though members of our laboratory staff have been repeatedly examined for M and N during the past 3 years, in no case has a change in type been noted.

In Table 5 we have summarized the results obtained up to date on the heredity of the agglutinogens M and N. These data, which include 674 families with 1899 children, present 8 "exceptions" to the theory of Landsteiner and Levine. That these "exceptions" are undoubtedly due to illegitimacy will now be proven.

TABLE 5.—SUMMARY OF ALL DATA ON THE HEREDITY OF THE AGGLUTINOGENS M AND N.

Types of parents.	Types of children.			Totals.
	M+N+	M+N-	M-N+	
M+N+ × M+N+	256	113	93	462
M+N+ × M-N+	218	2	225	445
M+N+ × M+N-	305	260	3	568
M+N- × M-N+	181	0	2	183
M+N- × M+N-	1	157	0	158
M-N+ × M-N+	0	0	83	83
Totals	961	532	406	1899

This table includes:

64 families with 286 children by Landsteiner and Levine.¹⁰

131 families with 642 children by Wiener and Vaisberg.¹³

72 families with 192 children by Schiff.¹²

290 families with 577 children by Clausen,¹⁷ of which

102 families with 105 children had been previously reported with Thomsen¹⁶ and

117 families with 202 children by Lattes and Garrasi.²⁰

For medicolegal purposes the mechanism of heredity of the agglutinogens M and N may be summarized in two laws:

1. The agglutinogens M and N can never appear in the blood of a child unless present in the blood of one or both parents.
2. The combinations M+N- parent with M-N+ child, and M-N+ parent with M+N- child are impossible.

TABLE 6.—SUMMARY OF ALL MOTHER-CHILD COMBINATIONS.

Authors.	Number of mothers.	Number of children.
Landsteiner and Levine (families)	64	286
Wiener and Vaisberg (families)	131	642
Schiff (families)	72	192
Clausen and Thomsen (families)	290	577
Lattes and Garrasi (families)	117	202
Schiff (forensic cases)	525
Schiff (newborn)	566
Wiener, Rothberg and Fox	461	497
Totals	3487

A rigid test of the theory may be made by examining a large series of mothers and their children (to eliminate the possibility of illegitimacy), in order to determine whether or not exceptions to

the second law ever occur. In Table 6, therefore, we have summarized all the mother-child combinations that have been studied thus far. *In this series of 3487 cases, not a single exception to the theory of Landsteiner and Levine was found.* This proves conclusively that it is impossible for an $M+N-$ mother to have an $M-N+$ child, or *vice versa*. Since the agglutinogens M and N are independent of sex in their heredity, the same statement must also hold for the father. Exceptions to the second law in family studies that implicate the father must therefore be due to illegitimacy.

If we now analyze the 8 "exceptions" in Table 5, we find that 7 of them are "exceptions" to the second law implicating the father, and therefore must be due to illegitimacy, as the authors themselves believed. The eighth case, which was found by Wiener and Vaisberg, is an "exception" to the first law, and is also undoubtedly due to illegitimacy, since such exceptions due to illegitimacy are rather to be expected in studies on a large series of families.

Landsteiner and Levine, and Wiener and Vaisberg also examined their families for the Landsteiner blood groups. Landsteiner and Levine found 6 "exceptions" to the heredity of the 4 blood groups due to illegitimacy, whereas Wiener and Vaisberg found only 1, indicating that the morals of the people studied by the former authors were lower. Therefore, the fact that Landsteiner and Levine found 5 of the 8 "exceptions" of Table 5, whereas Wiener and Vaisberg found only 2, corresponds to the expectations.

On the basis of this large series of studies, the medicolegal application of the agglutinogens M and N for the determination of non-paternity is fully justified at present, together with the application of the classic blood groups. By the combined use of all 4 agglutinogens, A, B, M, and N, it is possible to exonerate one-third of all men falsely accused of paternity.

To illustrate the method of application, and also because blood groups have been so little applied in this country for the determination of nonpaternity, I shall quote my experiences in 5 cases:

Case Abstracts. CASE 1 (previously reported¹⁹).—The question arose in this case whether the husband or another man was the father of a child. The husband was willing to support the child regardless of its paternity, but the wife insisted that she would only live with the child's true father. Dr. A. A. Eggston grouped the bloods of all 4 individuals, but as both men belonged to Group A, no decision could be rendered. He therefore referred the case to me for the application of the agglutinogens M and N. By this method, the lover could be definitely excluded as possible father of the child, since he belonged to type $M-N+$, whereas the child belonged to type $M+N-$. Of the two men, therefore, the husband could only have been the true father. The complete results of the blood examinations were:

Blood of:	Group.	Type.
Husband	A	$M+N-$
Lover	A	$M-N+$
Wife	B	$M+N-$
Child	A	$M+N-$

It is an interesting illustration of human nature that the woman finally left her husband for the lover regardless of the paternity of the child.

CASE 2.—This case was referred to me by Dr. S. H. Polayes, since he could render no decision by means of the classic Landsteiner blood groups. In this case, a man who had relations with his wife before marriage, and who had married her when she told him she was about to give birth to a child, desired a divorce, and as an excuse claimed that the child (at the time 2 years old) was not his. The findings were:

Blood of:	Group.	Type.
Husband	A	M+N—
Wife	A	M+N+
Child	O	M+N+

Since such a combination of groups is entirely possible, it is impossible to determine whether or not the child is legitimate.

CASE 3.—In this case a woman charged a man with the paternity of her child. Although the man admitted having had relations with the woman, he claimed that other men had had relations with her at about the same time. The court ordered blood tests, and the bloods were shipped to me from New Haven. The results were:

Blood of:	Group.	Type.
Putative father	A	M—N+
Mother	O	M+N+
Child	O	M—N+

Here again it is impossible to tell whether or not the man is the father of the child.

This case is important, however, because it illustrates how these tests can be introduced into our courts, provided that the lawyers and judges are progressive enough. The judge who ordered the blood tests for this case (New Haven Court of Common Pleas) stated that this was a new question to him, but if the tests resulted so that the examining physician, upon proper qualification, could state that the defendant could not have been the father, it would be important evidence. The results of the tests in this case left the question open, but upon other evidence, the defendant was adjudged the father of the child.

CASE 4.—This case was referred to me by Dr. W. G. Flickinger. Because he had suspected his wife of infidelity for a period of years, a man desired to have blood tests performed on his wife, his 2-year-old son, and himself. He also had a 14-year-old daughter of whose legitimacy he felt certain. The results were:

Blood of:	Group.	Type.
Husband	A	M+N—
Wife	O	M+N—
Son	O	M+N—

Here again no decision could be rendered.

CASE 5.—After 8 years of married life, during which time she had had frequent intercourse with her husband but had failed to become pregnant, Mrs. X met and fell in love with Mr. Y. Soon thereafter a boy was born, and 3 years later a girl was born. At about this time Mr. X discovered the relations between his wife and Mr. Y. When Mrs. X expressed her desire to leave her husband for Mr. Y, Mr. X threatened to take the case to court, where the custody of the children would most probably be awarded to him. Mrs. X felt that the children were Mr. Y's, and finally persuaded her husband to have blood tests performed. It was found at that time

that the husband, wife, and two children all belonged to group O, and that the lover belonged to Group A, so that no decision was possible. Two months ago a third child was born, a girl; the boy now being 5 years old, and the second child 2 years of age. In order to effect a final solution of their problem, these people came to New York for complete blood tests. The results were as follows:

Blood of:	Group.	Type.
Husband	O	M+N+
Lover	A	M-N+
Wife	O	M+N+
First child	O	M+N+
Second child	O	M+N-
Third child	A	M-N+

It can readily be seen that the lover could not be the father of the second child; and that the husband could not be the father of the third child. No decision is possible concerning the first child. In this case, therefore, our blood tests have succeeded in determining the paternity of 2 out of 3 children; for we have indirectly proved that the second child was the husband's and the third child was the lover's.

CASE 6.—In this case (New Haven Court of Common Pleas) the use of blood-grouping prevented a miscarriage of justice. E. N. charged L. R. with the paternity of her child, and after a preliminary hearing L. R. was held for trial. Although the defendant repeatedly denied his guilt, the weight of public opinion was against him. The attorney for the defendant suggested blood-grouping tests, to which the man, woman and child were subjected. The results of the tests were as follows:

Blood of:	Group.	Type.
Putative father	A	M+N+
Mother	O	M+N+
Child	B	M+N-

Since a Group O mother cannot give rise to a Group B child unless the father belongs to Group B or Group AB, L. R., who belongs to Group A, could not be the father of the child. After conferring with her lawyer, E. N. decided to withdraw her charges, and judgment was rendered for the defendant.

It seems hardly necessary to emphasize the importance of employing the utmost care when applying blood grouping for medicolegal purposes, since errors in technique can only serve to discredit all this work, as well as bringing about grave injustice. When testing for the Landsteiner blood groups, errors are practically impossible if both cells and serum of each blood are examined (see Table 1). Several potent testing sera of each group should be used, and several control bloods of each group should be included in every experiment. The tests should also be performed upon two independent samples of blood.

With respect to the examination of the bloods for the agglutinogens M and N, as we have already pointed out, the technique is somewhat more involved than the technique of typing for the classic blood groups. It is therefore of the utmost importance that the tests in medicolegal cases be performed by experts, *i. e.*, individuals who have done a considerable amount of work in this field and particularly with the agglutinogens M and N.

Summary. The medicolegal application of the Landsteiner blood groups for the determination of non-paternity is urged on the basis of the experiences of European countries during the past 10 years. The application of the agglutinogens M and N of Landsteiner and Levine is also fully justified at present, on the basis of studies on families totaling more than 3000 children. The method of application is illustrated by actual experiences in 6 cases, in 3 of which valuable information was obtained.

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A CHEMICAL PECULIARITY OF PELLAGRA BLOOD (RAPID IODIN DECOLORIZATION).

PRELIMINARY NOTE.

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In diseases with protean symptoms alterations of the blood are frequent and are often sufficiently well marked to be of diagnostic value. Goldberger¹ has emphasized that many cases of pellagra are overlooked owing to the limitation of their symptoms, in contrast to the manifestations of the well-developed classical case.

To quote, "While there is danger that conditions not pellagrous may be diagnosed as pellagra, there is perhaps greater danger that pellagra will fail of recognition. It is important to keep in mind the possibility of pellagra in cases of 'neurasthenia,' 'melancholia,' 'chronic indigestion with spring exacerbations,' 'dysentery,' 'pernicious anemia,' 'eczema,' 'sunburn,' 'epileptiform seizures,' 'vaginitis,' and obscure abdominal pains suggesting diseases of the ovaries, appendix or gall bladder." A specific change in the blood of known pellagrous cases might, therefore, serve as a criterion for diagnosis of these obscure conditions mentioned above, and for those cases designated by various authors as "pellagra *sine* pellagra."

About 1 year ago the author noticed that the erythrocytes of pellagrous blood caused more rapid decolorization of iodine solutions than other human erythrocytes, whether normal or pathologic. After a series of experiments designed to test this observation, there was developed a technique which promises to be of value as a clinical laboratory test in the diagnosis of pellagra.

Reagents. *Alcohol-ether Mixture.* A mixture of 3 volumes of 95 per cent ethyl alcohol and 4 volumes of ether (commercial or anesthetic ether may be used; chemically pure ether has not been tried).

Iodine Solution. Accurately prepared Lugol's solution (5 per cent iodine in 10 per cent potassium iodide).

Color Standards. Prepare a 3 per cent potassium dichromate solution and from this make the following dilutions: 1 to 5, 1 to 10, 1 to 20, 1 to 40, 1 to 80, 1 to 120, 1 to 240. Place these standards in a series of test tubes of the same internal diameter.

Procedure. *Liquid Petrolatum.* Five cubic centimeters samples of normal or nonpellagrous (control) and of suspected pellagrous venous blood are withdrawn and quickly introduced into 15 cc. centrifuge tubes containing 5 cc. of liquid petrolatum. *The time of collection of each specimen must be recorded.* As each sample is collected, the tube is stoppered and shaken very vigorously until the blood is defibrinated. This may best be accomplished by striking the stoppered end of the tube against the palm of the opposite hand. The specimens are then allowed to stand for 30 to 45 minutes, after which they are again vigorously shaken and centrifuged at 1000 revolutions per minute for 5 minutes. Before the second shaking it is advisable to remove the stoppers momentarily to permit the entrance of air for adequate oxygenation. When the tubes are removed from the centrifuge three distinct layers may be distinguished, namely, an upper layer of fibrin and oil, a middle layer of serum and a lower layer of erythrocytes, leukocytes, etc., which the author shall designate the erythrocytic layer. If any sample has not been properly defibrinated, clots will be present in the lower layer. Such samples should be discarded. One cubic centimeter samples of the erythrocytic layers are now transferred by means of serum pipettes to test tubes of the same diameter as those of the standards. In the removal of these samples from the erythrocytic layer, care must be taken that no oil, fibrin or serum enters the pipette by capillary action as it passes through the two upper layers.

Exactly 1 hour after taking the venous blood specimen, add to the corresponding erythrocytic sample, slowly and without shaking, 5 cc. of the alcohol-ether mixture and stopper the tube tightly. After the alcohol-ether mixture has been added to all samples, let them stand for approxi-

mately 6 hours at room temperature (25° to 30° C.). At the end of this time add in rapid succession to each tube by means of an accurate micro pipette (Folin micro blood pipette or Kahn serologic pipette) a 0.1-cc. portion of the iodine solution. Mix gently and replace the stoppers.

As the mixtures stand there will be noted a gradual diminution of color in each tube, but a greater decolorization in the pellagrous samples. Within 3 hours the extract of pellagrous blood may be completely decolorized while other samples are not. The most constant difference occurs after the tubes have stood about 12 hours. At this time compare the colors of the alcohol-ether extracts with the potassium dichromate standards. The color range of these standards represents that of most samples which have stood 12 hours. Occasionally, however, a pellagrous sample may be completely decolorized, and other samples may be darker than the 1 to 5 standard.

Interpretation. On the basis of cases studied, if the color of the unknown matched that of a standard two shades lighter than the nonpellagrous sample, a mild condition of pellagra was apparently indicated. If it compared with a standard three shades lighter than the normal, a moderately developed condition of pellagra was considered to be present. If the unknown compared with or was lighter than the fourth tube from the nonpellagrous or normal, advanced severe pellagra existed. Often in severe cases of pellagra the extract was completely decolorized at the end of or before 12 hours. Reactions have been designated, according to the above method of interpretation, as mild, moderate, severe and negative.

Conclusions relative to the interpretation of the test have been reached by a study of over 150 hospital and dispensary cases, including a variety of diseases, 50 of which were pellagrous. In this series it was found that definitely diagnosed untreated pellagra cases always gave very positive reactions. No other pathologic condition gave positive reactions except certain cases with varied complaints and obscure diagnoses, and other cases with variable complaints in which pellagra was suspected by the attending physician. Only 5 cases of definitely diagnosed pellagra which gave positive reactions were tested after treatment with yeast. In these cases, after an average of 1 month's treatment with yeast the reaction changed from severe to mild, or negative. Mild reactions were given only by treated cases of definitely diagnosed pellagra, and by some suspected cases which were not definitely diagnosed. Moderate reactions occurred in some of the suspected and undiagnosed cases, in some of the untreated pellagrins, and in some treated cases of pellagra. Severe reactions occurred only in definitely diagnosed, untreated cases of pellagra, in 3 of the suspected pellagra cases, and in some undiagnosed cases in which pellagra was not suspected. The following table gives a summary of conditions tested.

In the suspected and in the undiagnosed cases giving positive reactions, it is my belief that pellagra probably existed. It is in

TABLE 1.—RESULTS OF IODIN DECOLORIZATION TEST.

Diagnosis.	Reaction.	Number of cases.
Definitely diagnosed untreated pellagra . . .	Moderate to severe*	37
Definitely diagnosed treated pellagra, treatment of 2 to 4 months' duration . . .	Negative to mild and moderate reactions	10
Suspected pellagra, not definitely diagnosed	Mild to moderate and severe	6
Active pellagra complicated by other diseases	Severe	3
Undiagnosed cases, pellagra not suspected . .	Moderate to severe	8
Undiagnosed cases, pellagra not suspected . .	Negative	4
Addison's disease	Negative	1
Carcinoma of the pancreas	Negative	1
Epidemic encephalitis	Negative	3
Lateral sclerosis	Negative	1
Arterial hypertension	Negative	3
Tuberculosis of the lungs	Negative	5
Syphilis	Negative	5
General paresis	Negative	14
Tabes dorsalis	Negative	1
Dementia precox	Negative	20
Manic-depressive	Negative	4
Granuloma fungoides	Negative	1
Pernicious anemia	Negative	3
Diabetes mellitus	Negative	3
Myocardial disease	Negative	4
Multiple arthritis	Negative	4
Cirrhosis of liver	Negative	1
Acute bronchitis	Negative	2
Carcinoma of rectum	Negative	1
Psychoneuroses	Negative	4
Hyperthyroidism	Negative	2
Psoriasis	Negative	3
Carcinoma of cervix	Negative	1
Carcinoma of stomach	Negative	2
Myelogenous leukemia	Negative	1
Chronic nephritis	Negative	3
Ulcerative colitis	Negative	1
Normal	Negative	6
Total		168

* Reaction after treatment: Five cases observed and all became mild or negative after treatment.

these cases that the test would be especially valuable, and it remains for experience with the test to determine the reliability of the procedure as a criterion of diagnosis.†

† We feel that this preliminary note should be supported by the following statement which did not come to us through the author. Dr. M. R. Everett, Professor of Biochemistry and Pharmacology at the University of Oklahoma, has replied to our letter as follows: "A theoretical consideration of the possible pathology of glutathione metabolism in pellagrins led him to investigate the effects of iodine on the blood of hospital patients. . . . During this work I was almost a constant observer of his technique and to me the results were very striking, pellagrous samples of blood being easily distinguished from all the others, as described in his paper. Often series of samples were numbered and kept as unknowns until the laboratory tests were completed. . . . Dr. Campbell had some of his associates do the technical work of the test to provide a further check. In fact, I am certain that the only possible error in his test would have to be some insidious factor, such as an unknown impurity in his reagents (and, of course, we used various samples of reagents) but, of course, this could only be found by others trying the test. . . . Also Dr. Campbell has had the clinical advice and aid of some of our best clinical associates here. . . ."

Discussion. A detailed discussion of the possible chemical basis of this test must be postponed. Apparently the essential factor is a catalyst, since it is merely the rate of disappearance of the iodine which serves for differentiation. After a sufficient length of time both pellagrous and nonpellagrous extracts are totally decolorized. The very gradual reduction of the iodine in the above procedure points to something other than glutathione as the pertinent reducing factor. This has been substantiated by glutathione determinations in a number of these pellagrous bloods by the method of Woodward and Fry.² The glutathione content of these samples was found to be practically the same as that of the normals.

Delaville and Kowarski³ state that there are two fractions in blood concerned in the reduction of iodine, namely, a rapid one which they believe to be glutathione and a slow fraction, extremely complex, which reduces iodine at a very variable rate. My experiments have shown that the factor responsible for the gradual decolorization of iodine in the alcoholic-ether-erythrocytic mixture was constantly more active in pellagrous samples. Attempts have been made to simplify the procedure of the test described by using oxalated blood, laked corpuscles and whole blood. The results were unsatisfactory and the more complicated procedure described above is the only successful one thus far devised. Further study is in progress.

Conclusions. Pellagrous blood reduces iodine solutions at a constantly greater rate than that of any other blood thus far examined. This phenomenon is made the basis of a test which promises to be of clinical value in the diagnosis of pellagra. Many pathologic conditions have not been examined, and it is possible that further work will disclose that other conditions simulating pellagra may give positive reactions. However, the phenomenon of increased rate of iodine decolorization by the erythrocytes in pellagrous blood may lead to fruitful information bearing on the etiology of pellagra, certain entities of avitaminosis and malnutrition.

NOTE.—Appreciation is extended to administrative and faculty members of the University of Oklahoma School of Medicine and to the Superintendent of the Western Oklahoma State Hospital for the privileges of studying clinical material and for the use of laboratory facilities; also to Dr. M. R. Everett for helpful suggestions.

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MAINTENANCE OF NORMAL BLOOD IN PERNICIOUS ANEMIA BY MEANS OF INTRAMUSCULAR INJECTIONS OF A SOLUTION OF LIVER EXTRACT.*

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In a patient with pernicious anemia the maintenance of an essentially normal condition of the blood and a satisfactory state of health with sufficient liver substance to prevent a relapse is quite as important as that of treating the patient whose blood is in a state of relapse.

This paper deals particularly with the problem of the maintenance care of those patients treated with intramuscular injections of the Solution Liver Extract (Lederle), described in a previous paper.¹ One hundred and one patients have been treated in this manner during a period of 16 months. Six received the extract intravenously at some time during the period of observation. A few of the patients have taken liver or liver extract (fraction G of Cohn) by mouth in place of the injections for varying periods of time, and rarely small amounts of liver substance have been ingested in addition to that received by injection.

Of the 101 patients under discussion 44 received their first parenteral treatment during the time that they were patients in the hospital, and in the majority the blood was in a state of relapse. Fifteen patients who first came under observation with red blood cell counts under 4,000,000 per c.mm. were treated as ambulatory patients. The remaining 42 patients were changed to this form of treatment, having previously been under observation on a regimen of liver or liver extract by mouth. The change in form of therapy was frequently made at the patient's request, or particularly in those patients whose initial blood level was below normal, either because oral treatment was neglected or because a normal blood level was not maintained readily by means of the ingested liver substance. The entire group of patients reported represents a consecutive series and includes many definitely resistant cases.

Method of Treatment. The usual and advised procedure has been to give an initial subcutaneous injection of 0.2 cc. of solution followed in 1 hour by a similar injection of 0.4 cc. If by the end of 1 or 2 hours no evidence of sensitivity (indicated by a chill and rise in temperature) has appeared, a deep intramuscular injection, consisting of 6 cc. of solution

* This study was aided by a grant from the De Lamar Mobile Fund of the Harvard Medical School.

prepared from 200 gm. of liver, is given. At any time during the next 12 hours a second similar injection is given. At an interval of from 1 to 4 weeks after the initial therapy just described injections are resumed in 3-cc. doses* (prepared from 100 gm. of liver) at weekly intervals until the blood has reached a normal level (5,000,000 or more red blood cells), and then at intervals as indicated by the requirements of the individual patient. An effort has been made to extend the interval between injections only when the level of the blood count and the patient's condition warranted such a change. The presence of symptoms associated with spinal cord damage has been used as an indication for intensive treatment, even though the blood level was high. With such a policy in mind, and counting the number of red blood cells at the time of each intramuscular injection, it has been possible to extend the interval between injections to as long as 6 weeks and still maintain the patient and his blood in a satisfactory condition.

The intramuscular injections are given usually into the gluteal muscles, care being taken to avoid the region of the large bloodvessels and nerves. A 1.5-inch, 21-gauge needle is inserted by means of a quick thrust which renders the procedure essentially painless. The syringe containing the solution of liver extract is fitted to the needle, the plunger withdrawn slightly to be sure that blood cannot be withdrawn, and then the solution is injected slowly. In the event that blood appears in the needle it is to be withdrawn and reinserted.

Iron, usually in the form of capsules of ferric ammonium citrate,† has been given in doses of 3 gm. daily for varying lengths of time at some period during the course of treatment of the majority of the patients. With the rapid production of red blood cells, which occurs during the course of this form of treatment, the available iron reserve is depleted with a resulting apparent "secondary" anemia. This striking relative insufficiency of hemoglobin has occurred rarely in those patients ingesting whole liver, probably because of the iron contained therein, and because of slower regeneration. Generally the use of 100 to 200 gm. of ferric ammonium citrate given in the dose mentioned above is sufficient to bring the hemoglobin content of the cells to normal, and rarely is a second course of treatment necessary. Notable improvement in the patient's general condition, and particularly in the symptoms generally considered to accompany nerve damage, has occurred coincidentally with the use of iron.

Treatment During Relapse. Although a discussion of the results of treatment by means of the intramuscular injection of the solution of liver extract during relapse was presented in a previous paper,¹ the results obtained in a much larger group are now available. Satisfactory improvement in the condition of the patient and of the blood has occurred in each instance. There has been, however, considerable variation in the amount of solution used and the time interval necessary in order to bring the red blood cell count and hemoglobin to normal levels. These variations are to be expected and depend upon various circumstances relative to the patient's condition.

* The dose advised refers only to Solution Liver Extract (Lederle) which was used in each instance. Inadequate dosage must be avoided if less concentrated extracts are used.

† Capsules of Ferric Ammonium Citrate (Lederle), 0.5 gm. each.

The 44 patients first treated in the hospital had initial red blood cell counts varying between 1,000,000 and 4,500,000; 10 have either been discharged to other physicians or have been followed for only short periods of time; 34 have been followed for a period of time sufficient for the red blood cells to reach a level of 4,500,000 or more. In order to accomplish this the number of injections of extract derived from 100 gm. of liver (usually 3 cc.*) given generally varied from 5 to 10 and over periods of time varying from 20 to 50 days. The extremes varied from 2 injections in 10 days to 24 in 177 days. The longer periods of time and larger amounts of material were needed in those patients having complicating conditions.

Those treated as ambulatory patients have remained actively at work, some at hard manual labor, throughout their course of treatment. All 15 of this group whose initial red blood cell counts varied between 2,100,000 and 4,000,000 have also been followed until the red blood cell level was 4,500,000 or more. Ten reached this level in from 7 to 50 days and all but 2 in less than 60 days. The amount of liver extract used varied from 1 injection of 3 cc. (derived from 100 gm. of liver) to 8 such injections, except that 1 patient received 13 such injections in a period of 89 days.

In view of the fact that rest is generally considered to be important for the most satisfactory improvement of the blood, it is interesting to note the rapid improvement and the small amount of liver solution used intramuscularly in the ambulatory group. Because the results of treatment have been so little, if at all, retarded by activity it would seem advisable to allow a greater amount of activity for the patients treated in relapse in the hospital, especially the older ones in whom pulmonary complications and phlebitis must be guarded against.

Maintenance Treatment. The aim has been to establish for each patient the optimal treatment necessary for his or her needs and also to be as economical as possible in the amount of material used. It is vastly more important to the patient to be kept in good health than it is to attempt to economize by the use of minimal or sub-optimal doses. As with the use of liver substance by mouth, the proper dosage must be determined by the condition of the patient and by the trend of the red blood cell count as recorded at intervals over a period of time. The red blood cell level should remain preferably at or above 5,000,000 cells per c.mm., and the cells themselves should be normal in size and shape. Although the occurrence of symptoms of illness is an important indication of inadequate treatment, the absence of symptoms or a feeling of well-being is neither sufficient evidence that the blood is remaining

* In all but a few of the earlier injections this has been 3 cc. of solution. The earlier solution used and described previously was less concentrated.

normal nor that the patient is in satisfactory condition to avoid progression of the nerve disturbances.

The group of patients under observation has been maintained in a generally better state of health than a similar group observed under oral treatment. This fact is probably to be explained by the relative ease of administering optimal amounts of effective material in a manner favoring better absorption and utilization of the active substance and by the avoidance of gastrointestinal symptoms frequently observed in patients under treatment with liver by mouth, rather than on the basis of some unusual effect of the solution of liver extract. As was noted in a previous paper,¹ improvement in the symptoms occurring with peripheral nerve damage or spinal cord sclerosis has been unusually striking. This effect is no doubt also the result of the rapid and marked improvement possible through the ease of administration of adequate amounts of liver substance by the intramuscular route.

Eighty-one patients have been observed over a sufficiently long period of time to give one a clear idea of their maintenance requirements. This group is made up of 27 of the 44 patients first treated while in the hospital, 12 of those treated as ambulatory patients whose initial red blood cell counts were below 4,000,000, and 42 patients in whom the intramuscular treatment was introduced in place of some other. The red blood cell count when intramuscular treatment was started in the last mentioned group of 42 patients varied between 3,800,000 and 6,800,000. In 20 instances the count was below 4,500,000, and in 13 it was 5,000,000 or more.

In a few instances the lower blood levels in this group were due to failure on the part of the patient to follow out the prescribed treatment either because of an inability to obtain liver or a potent substitute for it, or a temporary inability to ingest it. The majority of those whose recorded initial blood level was below normal were taking average or even unusually large amounts of liver substance by mouth, with failure to maintain a satisfactory physical or blood condition. The difficulty to maintain readily a satisfactory condition with reasonable amounts of material has been due to the presence of chronic infections, arthritis, marked spinal cord sclerosis, unusual worry or perhaps old age. In the remainder of the patients of this group the change to intramuscular treatment has been made in order to influence favorably the difficulties occurring with spinal cord sclerosis, at the request of the patient, usually because of difficulty with the ingestion of the prescribed amount of liver, or through a desire to lessen the expense of treatment.

Typical examples of the manner in which treatment has been carried out in the patients under discussion are shown in Table 1. The red blood cell counts and hemoglobin levels recorded represent only the last determination made before a change to another treatment interval.

The number of patients receiving an injection of 3 cc. (derived from 100 gm. of liver) of the solution of liver extract at the various time intervals is shown in Table 2, together with the extremes and averages of the red blood cell levels in the patients treated at the several intervals.

TABLE 1.—THE MAINTENANCE TREATMENT WITH INTRAMUSCULAR INJECTIONS OF SOLUTION OF LIVER EXTRACT AS CARRIED OUT IN 81 PATIENTS WITH PERNICIOUS ANEMIA.¹

Case No.	Initial.		7 days.			14 days.			21 days.			28 days.			35 days.		
			No. 7-day intervals.	Resulting.		No. 14-day intervals.	Resulting.		No. 21-day intervals.	Resulting.		No. 28-day intervals.	Resulting.		No. 35-day intervals.	Resulting.	
	R.B.C.	HB.		R.B.C.	HB.		R.B.C.	HB.		R.B.C.	HB.		R.B.C.	HB.		R.B.C.	HB.
64	4.6	14.5	3	5.2	16.3												
67	4.2	12.8	7	5.6	15.2	3	5.4	14.5									
78	4.3	12.1	3	5.0	13.5	4	5.1	13.9	4	6.1	15.9						
85	4.5	11.7	4	5.2	14.3	5	5.1	14.1				3	5.3	16.3			
92	4.1	13.5	4	4.9	12.8	2	5.2	13.9	2	5.1	14.4	2	5.3	14.1

R.B.C. = red blood cells in millions per cubic millimeter.

HB. = hemoglobin in grams per 100 cc. of blood.

¹ Injections of 3 cc. extract prepared from 100 gm. liver given at the recorded interval.

TABLE 2.—THE INTERVALS BETWEEN TREATMENTS AND THE RED BLOOD CELL COUNTS MAINTAINED WITH INTRAMUSCULAR INJECTIONS OF SOLUTION OF LIVER EXTRACT IN 79 PATIENTS WITH PERNICIOUS ANEMIA.

Interval between injections, weeks.	Number of patients.	Range of final red blood cell counts.*	Average red blood cell counts.*
6	3	4.8-5.7	5.2
5	8	4.6-6.4	5.5
4	11	5.1-6.4	5.6
3	22	4.7-6.1	5.5
2	24	4.5-6.2	5.1
1	11	4.6-5.5	5.2

* In millions per c.mm.

One other patient with an initial red blood cell count of 2,380,000 received injections of solution totaling that obtained from 1000 gm. of liver in a period of 39 days. She has received no further treatment with liver substance during a period of 500 days, during which time her red blood cell count has varied from 5,100,000 to 8,400,000, and the hemoglobin has averaged 16.4 gm. per 100 cc. of blood. Another patient, whose initial red blood cell count was 3,480,000, received 11 injections representing the solution derived from 1100 gm. of liver in 62 days. No further liver treatment has

been received by the patient during a period of 308 days, during which time the red blood cell count has varied between 4,800,000 and 6,100,000 cells and the hemoglobin level has averaged 15 gm. per 100 cc. of blood.

The patients still under treatment at 7- or 14-day intervals have been under treatment generally for shorter periods of time than those receiving treatment at less frequent intervals.

Treatment has been very conservative, and the red blood cell levels have been maintained almost constantly above 5,000,000. In many instances it would no doubt be possible greatly to increase the interval between injections, but for one reason or another this has not been as yet deemed advisable. Because of extraordinarily high red blood cell levels in 2 patients, it has been possible to discontinue treatment for long periods of time. This may prove to be possible in other cases under this form of treatment, but, of course, should only be done when red blood cell counts can be made at frequent intervals.

Storage in the body of the substance active in stimulating formation of the red blood cells is suggested by the result obtained in these 2 patients. Richter, Ivy and Kim⁴ have presented evidence which suggests that the liver may have the ability to store the "active principle" of liver, which is in line with the opinion previously expressed by the author⁵ that "disturbances in the biliary system or liver may be of even more immediate etiologic importance (in pernicious anemia) than are the gastric changes." Another feature of the treatment has been the frequent occurrence of a steadily increasing red blood cell count as the interval between injections was increased. This suggests that any excess of the active substance over that which is actually used for the immediate production of blood is stored for future utilization.

Reactions. Reactions or complications following the intramuscular injection of the solution of liver extract have been negligible and of little practical importance in this series of cases treated with nearly 1000 injections. Two patients reacted after the first injection, one a small intracutaneous dose, in such a manner that sensitization to liver was suspected. After a series of small doses in increasing amounts both have continued the injections uneventfully. One patient developed urticaria with nausea following the 12th injection given on a very hot day. Very slight urticaria occurred following the next 2 injections, but has not occurred since. This patient first presented herself for intramuscular treatment with generalized urticaria, which had appeared following the ingestion of 2 vials of liver extract (Cohn fraction G). Hare,² Strandell and Hammar³ and others have reported urticarial rashes following the intramuscular injection of various liver extracts. On a few occasions the patient has felt faint after the injection. This has occurred in unusually

nervous persons who have received many other injections without such an occurrence. Hematoma has occurred at the site of injection twice. Infection has not occurred.

Results and Conclusions. Intramuscular injections of the solution of liver extract, given to patients in relapse or whose condition was unsatisfactory because of complications, instigated a remission in each instance, as is to be expected with treatment by means of the ingestion of liver or an actively potent substitute. The beneficial effects of intramuscular injections occurred sooner and more strikingly than with peroral treatment.

Maintenance treatment carried out by the same means in 81 instances for sufficiently long periods of time to allow analysis of the amount of solution needed, shows that an intramuscular injection of the amount of solution derived from 100 gm. of liver (generally 3 cc.), at intervals varying from 1 to 6 weeks, has maintained all of these patients in a satisfactory state of health with a normal condition of the blood. Improvement in the symptoms generally considered to accompany spinal or peripheral nerve damage has occurred regularly and often strikingly, and progression of these disturbances has not occurred in any patient after the blood condition has become essentially normal. Relapse has not occurred in any patient continuing under observation and treatment.

The anemia diet, but not including liver, as previously suggested for the patient with pernicious anemia, has been advised in each instance, and a course of large daily doses of iron (ferric ammonium citrate) has generally been prescribed at some time during the course of treatment, in order to allow the hemoglobin level to keep equal with the course of the rapid red blood cell formation. This has been of distinct benefit in improving the physical condition of the patient.

It has been possible with the use of the intramuscular treatment to maintain this group of patients in a better state of health and with a more satisfactory condition of the blood than was possible by means of treatment by mouth; the prolonged treatment has been more economical to the patient; and this method of administration of liver substance has usually been better liked.

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A STUDY OF A LYMPHOCYTIC HEMOGRAM.

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ARNETH,¹ in his monumental work on the polymorphonuclear leukocyte, laid the basis for subsequent studies on the nuclear changes in the granulocyte, culminating in the useful and well-known Schilling index. He also published an index of nuclear variation in the lymphocyte, to which he attached maturative significance. These studies, however, have not been verified.

In a recent article Wiseman² has reviewed the criteria of the age of lymphocytes and has classified them as follows:

1. Basophilia of the cytoplasm. The association of basophilia of the cytoplasm with the youth of other blood cells is well known. The so-called reticulocyte is an example of this characteristic in the immature erythrocyte. Basophilia is also well illustrated in the myeloblast and megaloblast.

2. Mitochondria. Cowdry³ states that as the cell matures, the number of mitochondria diminishes.

3. Size of the cell. This is a subject of considerable controversy, and some authors^{4,5} have regarded the large lymphocytes as the younger, while others^{6,7,8,9} have considered the small lymphocytes the more youthful. Most investigators studying fixed stained preparations call the large cells older, while those who use supravital technique hold the reverse.

4. Miscellaneous features, such as motility, vacuoles, chromatin content of the nucleus, proportion of nucleus to cytoplasm, shape of nucleus and azure granules.

Wiseman² studied normal bloods and those in which he would expect a physiologic or pathologic hyperplasia of lymphoid tissue, such as new-born rabbits and rabbits with active tuberculosis. The degree of basophilia in fixed preparations and the number of mitochondria by the supravital method in the same drop of blood were found to agree. He also found that the shape of the nucleus bears no relation to the degree of basophilia or the number of mitochondria. The chromatin content of the nucleus was not greatest in those cells which were least basophilic. Nucleoli, however, were visible only in the nuclei of cells with deeply basophilic cytoplasm and fine chromatin. No cytoplasmic structure in the living lymphocyte could be identified with the azure granules of the fixed cell, and this suggests that these granules are a precipitation brought about by fixation, possibly evidencing some functional

TABLE 1.—NORMALS.

Case.	Sex.	Age.	Diagnosis.	Date.	W. B. C.	Neut. polys., per cent.			Lymph., total per cent.	Lymph., per cent.		Mon., per cent.	Eos., per cent.	Bas., per cent.	Clinical data.
						Young.	Band.	Mature.		Yg.	Med. Ord.				
1	M	20-40 1-12 1-12 mos. 32	Average of normal adults Average of normal children Average of normal infants Normal	..	7,000	..	4	63	25	5	50	45	1	0	25 cases.
				..	8,000	..	2	41	50	10	60	30	1	1	25 cases.
				10/6	10,000	..	2	28	50	10	65	25	2	1	25 cases.
				10/8	7,000	..	1	69	23	17	45	38	..	1	Well.
				10/12	7,000	..	3	75	14	14	72	14	2	..	Head cold; temp. 100°.
2	F	30	Normal	10/14	4,800	64	32	15	59	26	2	..	Well.
				10/14	5,200	54	38	6	55	39	..	1	Well.
				10/29	6,800	..	1	57	35	8	54	38	Well.
				11/4	7,000	61	26	8	54	38	Well.
				10/15	8,000	..	1	61	30	3	41	56	Well.
				10/28	11,200	..	2	71	20	5	45	50	..	1	Well.
				11/4	8,100	..	1	58	35	9	66	25	Cold.
				11/9	9,600	60	33	11	58	31	4	..	Pains in abdomen for
				11/11	5,100	48	43	10	60	30	1	..	1 week; up and
				11/15	11,000	..	1	60	35	5	64	31	1	2	about.
				11/18	5,400	48	33	11	52	37	4	..	Well.

TABLE 2.—LEUKEMIC CASES.

Case.	Sex.	Age.	Diagnosis.	Date.	W. B. C.	Neut. polys., per cent.			Lymph., total per cent.	Lymph., per cent.		Mon., per cent.	Myelo- cytes, per cent.	Pre- myelo- cytes, per cent.	Myelo- blasts, per cent.	Clinical data.
						Young.	Band.	Mature.		Yg.	Med. Old.					
1	M	58	Lymphatic leukemia	10/15	200,000	..	2	13	85	95	5	0	Lymphoblasts, 34 per cent; died in 2 mos.
2	M	10	"	8/2	31,000	8	92	60	35	5	
3	M	55	"	9/3	42,800	25	73	39	51	10	2	
4	M	19	"	10/18	5,000	19	77	78	22	0	2	
5	M	60	"	7/20	140,000	7	92	0	100	0	1	Left hospital. Chronic type. Blasts, 20 per cent.
6	M	62	"	10/5	120,000	1	99	0	100	0	
7	M	59	Myeloid leukemia	10/22	170,000	..	2	2	96	0	97	3	
				10/29	150,000	2	98	0	95	5	
				11/5	150,000	2	97	0	96	4	1	
8	F	60	"	8/20	100,000	2	..	20	80	0	10	10	78	Acute form.
9	M	30	"	8/31	6,000	18	(on exam. many fields)	25	30	64	2	1	51	Subacute form.
10	M	45	"	9/12	30,000	8	14	35	65	0	5	22	73	Subacute form.
				9/20	300,000	15	20	24	(on exam. many fields)	8	80	12	17	..	2	Chronic form.

10	M	36	Multiple neuritis; etiology unknown	9/22 17,000 9/26 16,000 9/29 12,800 10/3 16,600 10/6 15,600 10/10 16,400 10/20 13,400 10/27 12,200 11/3 20,000 10/29 32,200 11/2 28,700 11/5 53,600 11/9 30,800 11/12 32,600	3	28	11	0	70	20	3	54	Temp. 101°; biopsies for trichiniasis negative. Temp. 100°.
11	F	52	Carbuncle of upper lip	10/29 32,200 11/2 28,700 11/5 53,600 11/9 30,800 11/12 32,600	17	71	6	15	68	16	6	..	Unimproved. Temp. 101°.
12	M	43	Inguinal adenitis	10/26 14,800 10/26 9,500 10/29 16,600 11/5 7,800 11/16 11,000 10/22 7,000 10/26 9,400 10/29 6,800	8	82	5	25	75	0	2	..	Progressively worse.
13	M	39	Typhoid?; broncho-pneumonia	10/29 6,800 11/2 7,400 11/5 8,600 11/9 5,600 11/12 4,000 11/16 5,400 10/22 26,200 10/26 19,000 10/29 16,400	2	71	17	12	50	38	5	..	Died. In hospital since 8/2, running septic temp.; biopsy of gland showed enormous proliferation of endothelial cells; temp. now between 99 and 100°, feels well. Temp. 101°.
14	F	41	Pneumonia; aneurysm of aorta or possible mediastinal neoplasm	11/5 8,400 11/9 18,800 11/12 6,600 10/21 16,400 10/25 24,000 10/28 23,800 11/1 13,400 11/4 15,000 11/10 9,800 11/17 15,400	0	61	34	22	56	22	10	..	History and Vidal suggestive of typhoid; developed signs in chest. Improved.
15	F	10	Chronic osteomyelitis of right femur	11/17 15,400 11/1 7,000 11/4 7,600 11/7 7,200 11/10 4,400 11/14 6,400 11/1 10,000 11/4 15,200 11/9 10,300 11/11 11,600 11/15 14,200 11/20 8,000	2	72	17	15	56	29	7	..	Improved. Temp. 102°.
16	M	48	Lobar pneumonia	11/17 15,400 11/1 7,000 11/4 7,600 11/7 7,200 11/10 4,400 11/14 6,400 11/1 10,000 11/4 15,200 11/9 10,300 11/11 11,600 11/15 14,200 11/20 8,000	1	68	19	31	47	22	9	..	Gradual improvement; temp. 100°. Slight relapse; temp. 103°.
17	F	21	Grippe	11/17 15,400 11/1 7,000 11/4 7,600 11/7 7,200 11/10 4,400 11/14 6,400 11/1 10,000 11/4 15,200 11/9 10,300 11/11 11,600 11/15 14,200 11/20 8,000	2	60	27	18	51	31	10	..	Improvement; temp. 100°. Temp. 100.5°.
					3	61	44	22	56	22	3	..	Temp. 101°; slight operation.
					4	63	26	3	57	40	5	..	Temp. 99°.
					5	59	27	27	59	14	6	..	Type I pneumococcus; temp. 103°.
					7	81	6	16	68	16	6	..	Improved.
					1	67	29	10	63	27	6	..	Up.
					4	50	40	35	45	20	5	..	Temp. 101.5°.
					1	45	45	13	70	17	5	..	Temp. 100°; menstruating.
					3	37	56	10	44	46	2	..	Improved; temp. 99°.
					7	81	6	16	68	16	6	..	Well.

activity of the mature cell. It, therefore, seems that basophilia of the cytoplasm is a constant and reliable criterion of the age of lymphocytes.

With these facts in mind studies were undertaken on a series of normal and diseased adults and children to see if a classification of lymphocytes according to the degree of basophilia would be of clinical value.

The cases selected were widely diversified and represented all types, from the very sick to ambulatory patients with minor complaints. In establishing the normals, single observations were used in the majority of instances. The sick patients were studied at bi-weekly intervals during their stay in the hospital, and a small series of normals were followed at similar intervals over a time interval corresponding to the average stay of a patient in the hospital.

This report embodies 75 normals, equally divided among adults, infants and children, 10 normals followed at bi-weekly intervals for 1 month and 150 patients followed at bi-weekly intervals during their stay in the hospital.

Technique. White and differential counts were done for each observation. The total white counts were done with carefully standardized pipettes, and the films were made on slides, care being taken to keep them "rim free." The stain used was Wiseman's Wright-Giemsa. An average of 200 leukocytes was counted and the lymphocytes were divided into three classes: Y (young), M (medium) and O (old) forms, according to the degree of basophilia of their cytoplasm. The Y forms have a deep blue cytoplasm, the M forms moderately blue and the O forms are faintly blue or colorless, and usually show azure granules in the cytoplasm, although the M forms occasionally show them too. A little practice with the above technique will make the three divisions clear. It is necessary, however, that the lymphocytes be examined in those parts of the film in which the red cells do not overlie, as in the thick portions of the film the lymphocytes are likely to overstain. The total number of lymphocytes is noted as well as the number of Y, M and O forms, and the percentages of each are then easily calculated, the procedure being similar to that followed in enumerating the different forms of polymorphonuclears when doing the Schilling index. When the total number of lymphocytes is low it is best to count 300 to 500 white cells to insure more accurate results. The polymorphonuclear leukocytes were tabulated according to the Schilling method in each instance in order to compare the granulocytic and lymphocytic indices.

The observations are to be found in the Tables, pages 279 to 281.

Discussion. Analysis of the experimental data shows that there is a fairly constant lymphocytic formula for normals. For adults this can be expressed as Y forms, 5 per cent; M forms, 50 per cent; O forms, 45 per cent. Variations occur in this formula under different conditions, and we can, therefore, speak of a shift to the left or to the right of the lymphocytic index, depending upon whether the number of younger forms is greater or less than normal. A comparison with the Schilling index in each case shows that the two do not run parallel. The lymphocytic index is not as stable as the Schilling and will shift to the left just as easily in a mild

as in an acute infection. Even though the lymphocytic formula cannot be used to gauge the severity of an infection, its shift to the left in these conditions nevertheless indicates that lymphocytes take an active part in combatting bacterial invasion. This is seen by the increase in Y and M forms and the decrease in O forms in practically all cases of infection.

The lability of the lymphocytic hemogram makes it valuable in the detection of minor infections which do not disturb the more stable Schilling index. Interesting and confirmatory evidence for using basophilia as a criterion of the age of lymphocytes is seen in the study of the lymphatic leukemias. The marked increase in the proportion of Y and M forms in these cases represents the well-known hyperactivity of the lymphatic system in these diseases. In the myeloid leukemias there is also an increase in lymphocytic activity and a shift of the index to the left.

It is also of interest to note that, according to the lymphocytic index, most patients are not entirely well on being discharged from the hospital and that the period of convalescence is probably much longer than usually expected. A patient should not be regarded as entirely recovered from an infection until the lymphocytic formula has returned to normal.

Conclusions. 1. A lymphocytic hemogram has been studied, using basophilia of the cytoplasm as a criterion of the age of the lymphocytes.

2. The lymphocytic formula is stable in health, but is more labile than the Schilling index, and cannot be used to gauge the severity of an infection. Its shift to the left in infections nevertheless indicates that the lymphocytes take an active part in combatting these conditions.

3. The lability of the lymphocytic index makes it valuable in detecting minor infections which do not disturb the more stable Schilling index.

4. The lymphocytic index is superior to the Schilling in guarding the progress of convalescence, and a patient should not be regarded as entirely well until the lymphocytic formula has returned approximately to normal.

Grateful acknowledgment is due Dr. J. S. Leopold for permission to study cases from the A. Jacobi Children's Division, Lenox Hill Hospital.

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REVIEWS.

A STANDARD CLASSIFIED NOMENCLATURE OF DISEASE. Compiled by The National Conference on Nomenclature of Disease. Edited by H. B. LOGIE, M.D., C.M., Executive Secretary. Pp. 701. New York: The Commonwealth Fund, 1933. Price, \$3.50.

THE names of the organizations and their distinguished representatives that have aided in or approved of this compilation are as good a guarantee of its value as such evidence can be. In passing one cannot help being curious why pathology was not included in the conference members or coöperating committees. Surely here is a field in which the pathologist has the last and most decisive say!

While one can naturally find many single items for objection, the general scheme is excellent. Using the decimal system throughout, a topographical classification (to 3 or more decimals) begins on page 14, giving 11 main systems (0, body as a whole; 1, integumentary; 2, musculo-skeletal, etc.). On page 50 begins the etiological classification, again with 11 subdivisions (0, prenatal; 1, lower parasites, etc., through x, "unknown or uncertain, the functional reaction to which alone is manifest"). Thus from the classified nomenclature proper (beginning on page 83) we learn for example that *talipes equinus* is listed as 249-0225, i. e., a disease of a joint (24) ninth to be listed, which is an abnormality of structure (02) due to distortion (022), the fifth to be listed (0225). The full index and especially "How to Use the Nomenclature" (page 11) should first be consulted.

E. K.

ENDOCRINE MEDICINE. In four volumes. By WILLIAM ENGELBACH, M.D., F.A.C.P., B.S., M.S., D.Sc., Member of Starr, St. Louis, City, Jewish, Baptist Sanitarium and Maternity Hospitals. With a Foreword by LEWELLYS F. BARKER, Professor Emeritus of Medicine, The Johns Hopkins University School of Medicine, Baltimore. Vol. I. General Considerations. Pp. 460; 139 illustrations and 62 tables. Vol. II. The Infantile and Juvenile Endocrinopathies. Pp. 473; 109 illustrations and 25 tables. Vol. III. The Adolescent and Adult Endocrinopathies. Pp. 562; 255 illustrations and 26 tables. Vol. IV. Bibliography, Index of Names and Subjects. Pp. 117. Springfield, Ill.: Charles C Thomas, 1932. Price, \$35.00 a set.

THIS is an elaborate treatise on endocrinology, with special emphasis placed on thyroid and pituitary, the author having reserved for the future a discussion (which his unfortunate death now prevents) of the islands of Langerhans and of Addison's disease.

Everyone must agree with the author's opening statement that "The recent advances made in the studies of the physiology and pathology of the endocrine glands are considered sufficient justification for compilation of a treatise endeavoring to bring this subject up to date." One would hope, too, that a four-volume work could give a satisfactory summary of the present knowledge of the various phases of this complex subject, even though doubting any one individual's ability to present all the different aspects satisfactorily. We must admire the author's courage, therefore, in undertaking the job single-handed, if not unaided, even though we may recognize that not a few questionable personal interpretations shake one's confidence in the value of the whole production.

Much of the literature is reviewed in a manner that is both careful and up to date, but the discussion is chiefly based upon the author's records of over 2000 patients with endocrine disorders. Thus the Fundamentals—whose advances constituted the "sufficient justification"—occupy but 200 of the 1800 pages of text. Furthermore the method of approach renders consultation arduous, even though the extensive index facilitates search for a given item. The segregation of the individual gland disturbances—often into different volumes—into disorders arising in Infants, Juveniles, Adolescents and Adults, makes a connected survey from the anatomical standpoint difficult and necessitates considerable repetition.

The work is profusely illustrated with photographs of patients, Roentgen rays, charts and detailed case histories. It is of interest in expressing the experience, convictions and classifications of the clinician author, and with its many references to the literature should be valuable to workers in this field.

E. K.

A MANUAL OF EMBRYOLOGY. By J. ERNEST FRAZER, F.R.C.S. ENG., Professor of Anatomy in the University of London; Lecturer at the Medical School of St. Mary's Hospital, etc. Pp. 486; 282 illustrations. New York: William Wood & Co., 1932. Price, \$8.00.

EVEN when existing textbooks on a subject are being kept reasonably up to date, a good new work is almost bound to bring a fresher point of view and give more adequate treatment to recent developments. In this case, the distinguished author is especially qualified to present the advances of the last quarter century in explaining the processes of development of human organs and tissues. The regional method of approach has been followed, as giving a better "connected mental picture of the developing embryo." Nevertheless a good index—and we commend the black face figures to indicate the chief treatment of a topic—permits one to use the book up to a certain point as a work of reference. All references, however, are omitted, statements made on the authority of others merely being indicated by the author's name in a bracket. Even for the medical student for whom the book is intended this constitutes a grave handicap for broad-minded study. However, even with this restriction, the book will prove useful in medical schools.

E. K.

MEN AGAINST DEATH. By PAUL DEKRUIF. Pp. 363; illustrated. New York: Harcourt, Brace & Co., 1932. Price, \$3.50.

LIKE the Microbe Hunters, Men against Death makes mighty good reading (so contagious is the author's style that an expletive unwittingly slipped in here, only to be replaced by the weaker adjective on re-reading!). We hope that a multitude of medical students and laymen will form the same opinion, so that they may become personally acquainted with more of the outstanding figures of our medical history. After this expression of our feelings, we hope that some objective criticisms will not be misunderstood.

A book which "pretends only to tell the plain story of scientific adventure for plain people" naturally must be evaluated by different criteria than a work of biography or history. We can pass over, then, more easily the colorful hyperbole and gratuitous expletives that are apparently deemed necessary to enliven the narrative, and, hoping that the facts have not been stretched to make a good story, can look forward to instructive entertainment. The author's prologue on the theme of his intense desire to live longer, like the cover advertisement that the book "is for all who want

to stay young as long as they can," should undoubtedly be read with the tongue in the cheek, but what odds to the modern reader, if amusing! Those described are: "Semmelweis: a tragic man afire to find a safe way to help mothers have their babies; Banting: brought new strength to people whose lives were running away in rivers of sugar; Minot: tricked pernicious anemia. Before him it was inexorably fatal; Spencer: found an unprecedented and fantastic way to guard men from spotted fever; Evans: removed one great danger lurking in the American milk supply; McCoy: fighting parrot fever alone, a general who did not want to die in bed; Schaudinn: discovered the pale horror of the sickness which along with cancer is one of humanity's two worst enemies; Bordet: spotted the pale horror's hiding; foretold doom for those neglectful; gave hope to all who'd fight their fate; Wagner-Jauregg: his friendly fever, now the electric fever of the new machine medicine, burns out paresis; Finsen: the Dane who trapped the light of the sun; Rollier: showed the folly of men spending millions to get themselves well when with free Doctor Sun they'd never start to be sick; Strandberg: turned Finsen's machine-sun on TB's most desperate consequence." The author has been able to amplify his sketches by personal contact with nine of the twelve subjects, which gives the reader a sense of closer contact than with the more remote figures of the Microbe Hunters.

E. K.

SCIENCE AND SUPERSTITION IN THE EIGHTEENTH CENTURY. A Study of the Treatment of Science in Two Encyclopedias of 1725-1750. Study No. 364 in Studies in History, Economics and Public Law, Edited by the Faculty of Political Science of Columbia University. By PHILIP SHORR, PH.D. Pp. 82. New York: Columbia University Press, 1932. Price, \$1.50.

To determine the amount of pseudoscience still clinging to science after the glorious 17th century, the author has examined the way in which science was handled in two representative 18th century encyclopedias—Chambers' Cyclopedia (London, 1728) and Zedler's Universal Lexicon (Leipzig, 1732-1750). Together with Thorndike's similar study of Diderot's Encyclopédie, these constitute "a key to the habits of thought" in science in the three leading countries of Europe. The two encyclopedias are considered separately, necessitating a certain amount of repetition and of division of attention. Thus although the treatment of astronomy by Pythagoras, the Arabians and so forth is considered in Chambers' work, the same has to be taken up again with variations in Zedler's. In medicine, we learn that the work begun by Vesalius and Harvey had had but little influence on scientific thought in overthrowing medieval Galenism—"The two encyclopedias still bear a close resemblance to their earlier medieval prototypes."

E. K.

ANLEITUNG ZUR FRÜHZEITIGEN ERKENNUNG DER KREBSKRANKHEIT. By various contributors. Pp. 134. Leipzig: S. Hirzel, 1932. Price, Rm. 3-.

THIS symposium on the early diagnosis of cancer has been written for the use of the general practitioner. It places the responsibility for the successful control of this disease in his hands. The early stigmata of cancer and certain general diagnostic procedures such as the sedimentation time are discussed first. There is next a very detailed review of cancer and sarcoma and its origin from the different epithelial and connective tissues. The larger part of the booklet is devoted to a detailed study of malignancy of every region,

organ and system of the body. Special stress is laid on a few early signs of cancer which should arouse the suspicion of the physician. Naturally the most frequent carcinomata such as carcinoma of the stomach, rectum, cervix and breast receive the most attention. The prognosis, without treatment and with early treatment, and the very earliest and most highly specialized diagnostic procedures are discussed at length. Such a dictum as: "The early diagnosis of malignancy in the small intestines is made by luck, in the large bowel by skill, and in the rectum as a matter of duty" is typical of the many of its phrases. It will be useful in the instruction of both student and general practitioner.

I. R.

ANTONY VAN LEEUWENHOEK AND HIS "LITTLE ANIMALS." By CLIFFORD DOBELL, F.R.S., Protistologist to the Medical Research Council, London; Foreign Member of the R. Accademia dei Lincei, Rome; Sometime Fellow of Trinity College, Cambridge. Pp. 435; illustrated. New York: Harcourt, Brace & Co., 1932.

THIS excellent work—the result of 25 years' personal study—comes opportunely from one of the leading protozoologists of his day on the 300th anniversary of the birth of the great Dutch microscopist. Finding commentaries more misleading than helpful, the author had chief recourse to Leeuwenhoek's copious correspondence in colloquial Dutch with the Royal Society of London, still extant in their archives. Tedious effort in mastering the difficult script (see Plate 5) as well as the archaic language has revealed much of interest about the man as well as his work that was not previously available. His letters from the first one, sent at the instigation of de Graaf, down to the last, sent on his deathbed a half century later, "contain observations on matters zoölogical, botanical, physical, physiological and miscellaneous (unclassifiable). They are mostly . . . concerned with observations and discoveries made with the microscope."

Following a hundred well-documented pages about Leeuwenhoek's life, methods of work, family relations, contemporary estimates and such like, come two hundred pages of translated letters, with numerous notes and comments. More notes on various personal items, including 27 "lost" letters found by Dobell, are followed by a critical evaluation of Leeuwenhoek's position in science, resulting in the conclusion, which would be hard to controvert, that he is justly regarded as the Father of Protozoölogy and Bacteriology. While the author's notes and comments would in themselves constitute a distinct contribution to the history of science, even more valuable are the original researches and translations now available for the first time. Dobell's successful attempt to preserve the quaintness of the original text, as far as compatible with maintaining the meaning conveyed by their originator, lends further charm to the presentation, still more added to by a strain of old-fashioned humor that pervades the comments and especially the Epistle to the Reader.

E. K.

OFFICE SURGERY. By FENWICK BEEKMAN, M.D., Visiting Surgeon, Bellevue Hospital; Visiting Surgeon, Hospital for the Ruptured and Crippled, etc. (Everyday Practice Series, edited by HARLOW BROOKS, M.D.) Pp. 402; 94 illustrations. Philadelphia: J. B. Lippincott Company, 1932. Price, \$5.00.

THE volumes in this series are prepared primarily for the general practitioner. The cover and format are well done. The author has aptly said

that "there is no such thing as minor surgery for any surgical lesion, be it ever so insignificant, may be the first sign of a serious condition." The form and style in which the subjects have been presented are not strictly conventional, but the author has attempted to "present a readable book." The material for use in an office, anesthesia, wounds, fractures and dislocations, infections, superficial neoplasms and lesions of the external genitalia, anus and rectum are covered in an interesting, terse fashion. The illustrations are good. This volume should prove a valuable addition to the literature of the student and general practitioner. I. R.

FUNCTIONAL DISORDERS OF THE LARGE INTESTINE AND THEIR TREATMENT. By JACOB BUCKSTEIN, M.D., Instructor in Gastro-intestinal Roentgenology, Cornell University Medical College, etc. Pp. 223; 60 illustrations and 40 reproductions of radiographs. New York: Harper and Brothers, 1932. Price, \$3.00.

THE author has been peculiarly successful in preparing a concise book on the functional disorders of the colon. Our understanding of this organ has been chiefly advanced in recent years by roentgenologic studies and full use of these is made throughout. Detailed instruction in the handling of patients is made to depend whenever possible upon the fundamental pathologic physiology as far as it is understood. Specific information which the practitioner requires is here readily accessible upon such subjects as constipation, enteroptosis, "irritability of the colon associated with mucus," gaseous distension, and the perennial question of chronic appendicitis. The symptoms generally attributed to these conditions are of such great frequency, and the conditions, themselves, so ill-defined, that the experimental approach to their explanation becomes particularly valuable. In the case of the colon, this has been difficult because of the inconsistency of response which characterizes that organ. The experimental data, therefore, are frequently contradictory, and one could wish that even at the expense of compactness the author might more frequently have given his own conclusions from the evidence he presents.

Taken as a whole, the book is well balanced, though one is occasionally surprised, as by the space allotted to studies of such debatable value as the roentgenologic diagnosis of chronic appendicitis. Nevertheless, it is a careful attempt briefly to clarify a very involved field of medicine.

W. O. A.

RADIOLOGIC MAXIMS. By HAROLD SWANBERG, B.Sc., M.D., F.A.C.P., Editor, The Radiological Review; Radiologist, St. Mary's Hospital and Blessing Hospitals, Quincy, Ill., etc. With a Foreword by HENRY SCHMITZ, A.M., M.D., LL.D., F.A.C.R., F.A.C.S., Professor of Gynecology and Head of the Department, Loyola University School of Medicine, etc. Pp. 125. Quincy, Ill.: Radiological Review Publishing Company, 1932. Price, \$1.50.

A LITTLE volume devoted to a heterogeneous collection of radiological principles gathered from the rapidly accumulating knowledge of the use of radium and the Roentgen ray. Included are numerous quotations from various medical authorities relative to the value of radiology and the position it now occupies in the realm of medical diagnosis and treatment.

K. K.

MANUALE DI ANALISI CHIMICA. By CESARE SERONO, Dattore in Medicina ed in Chimica; Docente in Chimica e Microscopia Clinica nella R. Università di Roma. In collaboration with PROFESSOR ALFONSO CRUTO. Pp. 483; 85 illustrations. Second edition, Torino: Unione Tipografico-Editrice Torinese, 1932. (Price not given.)

THE outstanding feature and advantage of this manual over similar publications is the general part dealing with elementary chemical procedures, containing data valuable to the laboratory worker. The special part covers complete chemical examination of blood, urine, feces and other excreta and secreta. In addition there are good chapters on food and water analysis, and analysis for the commonest poisons. M. S.

RESEARCHES ON BLACKWATER FEVER IN SOUTHERN RHODESIA. No. 6 of the Memoir Series of The London School of Hygiene and Tropical Medicine. By G. R. ROSS, M.B., CH.B., PH.D., D.P.H., Rhodesian Research Fellow, London School of Hygiene and Tropical Medicine. Pp. 262; illustrated with tables and charts. London: The London School of Hygiene and Tropical Medicine. Price: paper, 8s.; cloth, 10s.6d.

IN his interesting studies Dr. Ross brings out the epidemiology, blood changes, treatment, etc., in patients suffering with blackwater fever. There should not be any fixed outline of treatment, however, as no two cases are alike, and the author is of the opinion that each patient should be treated individually. D. DE R.

THE FAILING HEART OF MIDDLE LIFE. By ALBERT S. HYMAN, A.B., M.D., F.A.C.P., Cardiologist, Beth David and Manhattan General Hospitals, etc., and AARON E. PARSONNET, M.D., C.M., F.A.C.P., Attending Physician and Cardiologist, Newark Beth Israel Hospital, etc. With a Preface by DAVID RIESMAN, M.D., Sc.D., F.A.C.P., Professor of Clinical Medicine, University of Pennsylvania School of Medicine. Pp. 538; 166 illustrations, some in colors. Philadelphia: F. A. Davis Company, 1932. Price, \$5.00.

THE authors of this volume have limited themselves almost exclusively to a consideration of those cardiac manifestations that result from a derangement of the blood supply of the heart. The various phases of the subject have been fully and comprehensively discussed. The book is well made up and contains many good illustrations. The style is to be both criticized and commended; it is at times labored and involved and even redundant; but in spite of these handicaps, the book proves easy and pleasant to read.

Many of the conclusions are highly speculative. Some, particularly those based upon a wide application of the theory of functional stenocardia or coronary insufficiency, will not be definitely accepted at the present time by many students of cardiology. However, such hypothetical conceptions do no real harm if they are understood to be tentative; nor do they prevent the book from fulfilling its real purpose. This, as admirably set forth in the preface by Riesman, is to present comprehensively this very important subject to the general practitioner and "to maintain his confidence in himself while at the same time urging him to become acquainted as far as possible with the newer science of cardiology." This aim is well fulfilled. T. McM.

THE 1932 YEAR BOOK OF RADIOLOGY: DIAGNOSIS. Edited by CHARLES A. WATERS, M.D., Associate in Roentgenology, Johns Hopkins University; Assistant Visiting Roentgenologist, Johns Hopkins Hospital. THERAPEUTICS. Edited by IRA I. KAPLAN, B.Sc., M.D., Director, Division of Cancer, Department of Hospitals, City of New York, etc. Pp. 750; 498 illustrations. Chicago: The Year Book Publishers, Inc., 1932. Price, \$6.00.

In this volume is given a brief review of the principal American and foreign contributions made to radiologic literature during the past year. Of its two parts, the first is devoted to diagnosis and the second to therapy, edited by Drs. Waters and Kaplan, respectively. The authors have succeeded in presenting a concise and comprehensive résumé of the progress made in radiology during the past 12 months. Numerous illustrations and individual references to the original articles add materially to the value of this work. This volume should be appreciatively welcomed by those engaged in the practice of radiology, as it affords an excellent panoramic view of the present status of this specialty. K. K.

THE HISTORY OF DERMATOLOGY. By WILLIAM ALLEN PUSEY, A.M., M.D., LL.D., Professor of Dermatology Emeritus, University of Illinois; sometime President of the American Dermatological Association and of the American Medical Association. Pp. 223; 32 illustrations. Springfield, Ill.: Charles C Thomas, 1933. Price, \$3.00.

THE author, himself an eminent dermatologist, has produced for English speaking readers an account of dermatology that has previously been available only in such works as Puschmann's *Handbuch*, Richter's *Geschichte der Dermatologie* or in the short introductory chapters of textbooks or scattered through general medical histories. Believing that one should especially study the masters, he has included more than 300 individuals in the 9 chapters that chronologically divide the story of dermatology between 3000 B.C. and modern times. More than half the space is required for the 19th and 20th centuries, however. Though there is considerable space devoted to matters that have little to do with dermatology, this will doubtless not be objected to by the general reader. A novel and most useful feature is a 35-page Historical Index by Dr. Herbert Rattner, which without pretending to absolute completeness gives significant data about skin disease, arranged alphabetically. The book is in Thomas' accustomed high level of bookmaking, excellent paper, type (21 by 38 pica) and binding that makes it a delight to handle. It is, however, no exception to the dictum that the book without an error has never been printed. The illustrations are well chosen and for the most part excellent. E. K.

A GUIDE TO HUMAN PARASITOLOGY. By D. B. BLACKLOCK, M.D. (EDIN.), D.P.H. (LOND.), D.T.M. (LIVER.), Professor of Parasitology, Liverpool School of Tropical Medicine, the University of Liverpool, etc., and T. SOUTHWELL, D.Sc., Ph.D., A.R.C.Sc., F.Z.S., F.R.S.E., Lecturer in Helminthology, School of Tropical Medicine, Liverpool, etc. Pp. 271; 122 illustrations, and 2 colored plates. New York: William Wood & Co., 1932. Price, \$4.00.

THIS is a well-written, carefully arranged and unusually complete manual. The opening chapters are devoted to discussions of readily available sources

of material for study; simple but practical and accurate means of diagnosis; the mechanics of the microscope, and its care, calibration and use; methods of examining material such as blood, feces and urine for parasitic organisms; and general phases of parasitology and nomenclature. This is followed by sections on spirochetes, protozoa, cestodes, trematodes and nematodes parasitic in man. There is a chapter on myiasis and one giving tabulated summaries of life histories, vehicles of transmission, modes of infection, tissues involved and diagnostic characters. The last hundred pages contain notes on the therapy of parasitic diseases, a list of apparatus and reagents that may be of value, a short list of reference books and an index. The sections dealing with each group of organisms open with general statements, definitions, keys for identification and diagnostic methods. Each organism is discussed with regard to geographic distribution, habitat in the host, morphology, life history, pathogenicity and diagnosis of infection. Tabulated summaries of important facts are given at the end of each section. The illustrations are adequate. The diagrammatic life histories, of which there are 22, should be useful. Practicality is the keynote of the book. It affords a working knowledge of the subject, and is one of the best, if not the best, of its type that has come to the attention of the Reviewer.

H. R.

HABITS, THEIR MAKING AND UNMAKING. By KNIGHT DUNLAP, Professor of Experimental Psychology in the Johns Hopkins University. Pp. 326. New York: Liveright, Inc., 1932. Price, \$3.00.

MATERIAL in this work is divided roughly into two sections. The first portion presents the fundamental principles, the theories, the process and conditions of efficient learning. It is very interesting and easy reading and is presented largely from the viewpoint of the laboratory psychologist.

The second section attempts to correlate the earlier material with the breaking of specific bad habits. Bad habits such as stammering, masturbation, tics and homosexuality and other reactions supposedly of psychological origin are used as examples in demonstrating how the breaking of such habits may be carried out through a process of "negative practice," or "unlearning," in other words, a so-called reversal of the learning process.

The author's viewpoint is quite unique and certainly very extreme, and cannot be said to be fundamentally sound; for the detailed discussion of the technique of treatment and associated material does not indicate an unprejudiced knowledge of the deep motivations known to be back of such characteristics or habits. The chapter on the breaking of specific bad habits is particularly full of exaggerations and statements that are not supported by a *wide* "clinical" experience. The great simplification of this work, which is intended for the layman, may be responsible for some of the dogmatic tenor but it does not help an otherwise very novel presentation.

The extensive appendix and bibliography is excellently arranged in direct connection with the material presented in various chapters and can be said to be one of the most valuable portions of the book.

L. S.

EXPERIMENTAL ANALYSIS OF DEVELOPMENTS. By BERNHARD DÜRKEN, Professor in the University of Breslau. Translated by H. G. and A. M. NEWTH. Pp. 288; 120 illustrations. New York: W. W. Norton & Co., 1932. Price, \$4.75.

THE problems and methods of experimental embryology, and some of the results achieved, are here brought together in the form of a survey.

The experimental method in the study of development was used as early as the 18th century, but its modern phase dates from Wilhelm Roux (1850-1924). The material is mostly from the lower vertebrates, especially the amphibians, and from the invertebrates. The subject matter is considered under 8 chapters, such as fertilization and the stimulus to development, the problem of determination, and the influence of environment on the process of development. The number of problems which have already been studied in this comparatively new field is impressive. The details of these are of the greatest interest to the experimentalist and embryologist, but the results and the principles involved have a much wider appeal.

W. A.

BOOKS RECEIVED.

NEW BOOKS.

A Text-book of Neuropathology. By ARTHUR WEIL, M.D., Associate Professor of Neuropathology, Northwestern University Medical School, Chicago. Pp. 335; 260 illustrations. Philadelphia: Lea & Febiger, 1933. Price, \$5.00.

Urine and Urinalysis. By LOUIS GERSHENFELD, Ph.M., B.Sc., P.D., Professor of Bacteriology and Hygiene and Director of the Bacteriological and Clinical Chemistry Laboratories at the Philadelphia College of Pharmacy and Science. Pp. 272; 36 illustrations. Philadelphia: Lea & Febiger, 1933. Price, \$2.75.

Les Rythmes et la Vie. By MM. LAIGNEL-LAVASTINE, A. M. CHANOT, J. MONCHANIN, G. RICHARD, J. GUITTON, F. MENTRE, H. DUPRAT, H. CARDOT and R. BIOT. Pp. 264. Lyon: Librairie Lavandier, n.d. Price, 15 fr.

Le Nystagmus Vestibulaire et les Réactions de Mouvements. By R. CLAOUÉ, Professeur libre d'oto-rhino-laryngologie (Bordeaux). Pp. 64; 17 illustrations, 2 in color. Paris: Norbert Maloine, 1933.

Cerrico-vaginitis of Gonococcal Origin in Children. Report of a Project of The Bellevue-Yorkville Health Demonstration of New York City. By WALTER M. BRUNET, M.D., DORA M. TOLLE, M.D., SARA ALICIA SCUDDER, and ANNE RUTH MEDCALF. Foreword by EMILY D. BARRINGER, M.D., ROBERT L. DICKINSON, M.D., and WILLIAM H. PARK, M.D. Pp. 97; 11 figures, 11 tables and 1 colored plate. New York: Milbank Memorial Fund, 1933.

El Primer Centenar de Enfermos de Lepra Curados por el Dr. A. Bencheitrit. Pp. 144; 100 illustrations. Bogotá: Editorial Minerva, 1933.

The Vitamins in Health and Disease. By BARNETT SURE, Ph.D., Professor of Agricultural Chemistry, University of Arkansas, Fayetteville. Pp. 206; 4 tables. Baltimore: The Williams & Wilkins Company, 1933. Price, \$2.00.

Fighting Disease With Drugs. The Story of Pharmacy. A Symposium. Edited by JOHN C. KRANTZ, JR., with an Introduction by DR. JAMES H. BEAL. Pp. 230; illustrated. Baltimore: The Williams & Wilkins Company, 1931. Price, \$2.00.

Collected Reprints from the Laboratories of the Mount Sinai Hospital, New York, 1932. LOUIS GROSS, M.D., Director.

Ursachen und Behandlung der Krankheiten (causae et curae). By the Aebtissin Hildegard von Bingen. Translated by PROFESSOR DR. HUGO SCHULZ, Greifswald. Pp. 235. München: Verlag der Aertzlichen Rundschau Otto Gmelin, 1933. Price: Paper, Mk. 10.80; Bound, Mk. 13.

Studies in the History of Ophthalmology in England Prior to the Year 1800. By R. RUTSON JAMES, F.R.C.S. (ENG.), Consulting Ophthalmic Surgeon to St. George's Hospital and Senior Editor of the British Journal of Ophthalmology. Pp. 255; 9 plates. New York: The Macmillan Company, 1933. Price, \$4.00.

Diet in Sinus Infections and Colds. By EGON V. ULLMANN, M.D., Formerly Special Lecturer for Biology at the Oregon State College; Instructor at the First Medical Clinic at the University of Vienna, etc. Recipes and Menus by ELIZA MEZ. Pp. 166. New York: The Macmillan Company, 1933. Price, \$2.00.

Medicine in Canada. Vol. IX of *Clio Medica*. By WILLIAM B. HOWELL, M.D., Anesthetist-in-Charge, Royal Victoria Hospital; Lecturer in Anesthesia, McGill University, Montreal. Pp. 137; 6 illustrations. New York: Paul B. Hoeber, Inc., 1933. Price, \$1.50.

El Asma Y Otras Enfermedades Alergicas. By DR. CARLOS JIMENEZ DIAZ. Pp. 945; 88 illustrations, some colored. Madrid: Editorial España, 1932. Price, 60 pesetas.

The Biochemistry of Medicine. By A. T. CAMERON, M.A., D.Sc., F.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba; Biochemist, Winnipeg General Hospital, and C. R. GILMOUR, M.D., C.M., F.R.C.P. (C.), Professor of Medicine and Clinical Medicine, University of Manitoba; Physician, Winnipeg General Hospital. Pp. 506; 31 illustrations. Baltimore: William Wood & Co., 1933. Price, \$7.25.

International Clinics. Vol. II, *Forty-third Series, 1933.* Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with the collaboration of various contributors. Pp. 314; 31 illustrations, 1 colored. Philadelphia: J. B. Lippincott Company, 1933.

Hyperinsulinism, Pulmonary Hypertension, Stenosis of the Coronary Arteries, the Pathological Physiology of the Circulation, Hypertension, Abnormal Uterine Bleeding, Lymphogranuloma, Standards in Therapeutics, and Recent Progress in Obstetrics and Pediatrics are the subjects discussed in this interesting number.

The Clinical Aspect of Chronic Poisoning by Aluminum and Its Alloys. By LEO SPIRA, M.D., with a Foreword by PROFESSOR DR. HANS HORST MEYER, University of Vienna. Pp. 28; 1 illustration. London: John Bale Sons & Danielsson, Ltd., 1933. Price, 2/6.

Causal Factors in Tuberculosis. A Report of an Investigation into the Incidence of Tuberculosis in Certain Tyneside Districts. By F. C. S. BRADBURY, M.D., D.P.H., Medical Commissioner of Tyneside Inquiry. Pp. 126; various tables. London: National Association for the Prevention of Tuberculosis, 1933. Price, 2/-.

The Medical Clinics of North America, Vol. 16, No. 6 (*Mayo Clinic Number, May, 1933*). Index Number. Pp. 239; 28 illustrations. Philadelphia: W. B. Saunders Company, 1933.

A Laboratory Manual of Neuro-anatomy. Part II. Stereographic Plates. By C. L. DAVIS, M.D., Professor of Anatomy, University of Maryland, and H. S. RUBINSTEIN, B.S., M.D., Instructor in Neuro-anatomy and Assistant in Medicine, University of Maryland. Baltimore: William Wood & Co., 1933. Price, \$3.00.

"This series of stereograms was originally made for use in the teaching of neuro-anatomy at the University of Maryland Medical School. They represent an effort to provide the student at a minimum expense with a satisfactory substitute for the actual specimen. It is designed as an aid to laboratory study of the brain and for bringing to the study an adequate substitute for the specimens usually obtainable in the laboratory alone. Many structures which lend themselves to this method of demonstration are lacking, not because of greater importance of the structures shown but because, in limiting the scope of the work to a point which brings it within the reach of most students, certain structures were arbitrarily selected for demonstration and others omitted." (From authors' Introduction.) Part I, the book itself, will not be ready for publication for a considerable time.

The Heroic Age of Science. The Conception, Ideals, and Methods of Science Among the Ancient Greeks. By WILLIAM ARTHUR HEIDEL, Research Professor of the Greek Language and Literature in Wesleyan University; Research Associate of the American Council of Learned Societies of the Carnegie Institution of Washington. Pp. 203. Baltimore: The Williams & Wilkins Company, 1933, for Carnegie Institution of Washington. Price, \$2.50.

A German Doctor at the Front (Die Front der Ärzte). By PROFESSOR DR. WILHELM HIS. Translated from the Original German by COLONEL GUSTAVUS M. BLECH, Medical Corps, Reserve, and BRIGADIER-GENERAL JEFFERSON R. KEAN, Medical Corps, U. S. A. (Retired). Pp. 230; 1 illustration. Washington, D. C.: The National Publishing Company, 1933 (American Edition). Price, \$2.50.

Modern Aspects of Gastro-enterology. By M. A. ARAFA, M.R.C.P. (LOND.), Medical Assistant to Guy's Hospital, London; Medical Tutor to the Egyptian University and Formerly Senior Medical Registrar to Kasr-el-ainy Hospital, Cairo. With a Foreword by ARTHUR F. HURST, M.D., F.R.C.P., Senior Physician, Guy's Hospital, London. Pp. 374; 79 illustrations. Baltimore: William Wood & Co., 1933. Price, \$8.25.

Filterable Virus Diseases in Man. By JOSEPH FINE, M.D., B.Sc., D.P.H. (GLAS.), D.T.M. (LIVERPOOL), Assistant to the Professor of Public Health, Edinburgh University; Formerly Research Assistant, Sir Alfred L. Jones Laboratory (Liverpool School of Tropical Medicine), Freetown, Sierra Leone; Late Assistant Pathologist, Ancoats Hospital, Manchester. Pp. 144. Baltimore: William Wood & Co., 1932. Price, \$2.25.

NEW EDITIONS.

Surgical Pathology. By WILLIAM BOYD, M.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.), Dipl. Psych., F.R.C.S., Professor of Pathology, University of Manitoba; Pathologist to the Winnipeg General Hospital, Winnipeg, Canada. Pp. 866; 477 illustrations and 13 colored plates. Third edition thoroughly revised. Philadelphia: W. B. Saunders Company, 1933. Price, \$10.00.

This edition retains the excellences of former editions and this is intended as high praise. In addition to extensive alterations, new sections have been added on: metabolism of tumors, the goitrogenous action of cabbage, chronic follicular gastritis, developmental enterogenous cysts, lesions of the appendices epiploicae, Masson's musculonervous complex of the appendix, autolytic peritonitis, cholecystitis glandularis proliferans, high temperature deaths following cholecystectomy, obstruction of the common bile duct, non-obstructive hydronephrosis, injuries to the spleen, bloody discharge from the nipple, Cushing's syndrome, cysts of the semilunar cartilages, and the absorption of bone.

A Dictionary of Greek and Latin Combining Forms Used in Zoological Names. By EDMUND C. JAEGER, Head of the Department of Zoology, Riverside Junior College, Riverside, California. Pp. 157. Second edition. Springfield, Ill.: Charles C Thomas, 1931. Price, \$1.50.

The Art of Marriage. A Scientific Treatise. By J. F. HAYDEN, B.Sc. Pp. 218. Revised and enlarged edition. High Point, N. C. Book Sales Agency, 1931. Sales agent: The Union Library Association, New York. Price, 98 cents.

There is no question but that these topics like those of birth control should be available to the intelligent public.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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The Heart After Diphtheria.—The well known tendency for occasional involvement of the heart muscle and rare implication of the conduction system during the course of acute diphtheria has raised important questions in reference to this disease causing permanent heart damage. The first serious effort to make a study of the post-diphtheritic heart was made by White and Smith in 1905. Their cases were examined, however, only a comparatively few months after the patients were convalescent from diphtheria. Hoskin has also made an electrocardiographic examination in patients convalescing from the disease, while Jones and White 6 years ago examined 100 patients who had had diphtheria from 5 to 8 years previously. They could find no evidence of organic heart disease in patients who had had diphtheria with that length of time intervening. Sutherland agrees that diphtheria does not have a lasting effect on the heart, whereas Rolleston thinks that it does produce injury and Butler and Levine hold the same view in the instance of heart block. STANLEY ALSTEAD (*Lancet*, 1933, 224, 413) has reinvestigated the whole subject, studying a large number of children who have had diphtheria 1 to 10 years prior to the time of the examination. A considerable number of the cases were excluded for various reasons which might be instrumental in bringing heart changes as a result of some condition other than diphtheria. Ultimately 150 cases were selected for study. The average age of this group was 14 years. There were 21 (14 per cent) who had a history of clinical abnormalities in the heart during diphtheria. Only 2 of these had any symptoms or signs of cardiac lesion on reëxamination. Eight patients presented signs and symptoms suggestive of cardiac abnormalities but 2 of these cases were subsequently omitted because the cardiac abnormality was of doubtful importance. In reviewing the brief case reports of these 8 cases it seems that there are 2 or 3 others which might well have been omitted, but aside from that, accepting the author's diagnosis, only 3.3 per cent of the series showed clinical evidence of heart abnormality and, of these, only 2 showed abnormal electrocardiograms. In the group as a whole, the electrocardiograms as contrasted with 100 control cases were virtually the same if such differences as occurred are considered to be caused by chance factors. The only exception to this was that in 90 of the cases of diphtheria there was a negative or isoelectric *T* wave, which abnormality may

or may not mean very much and is of doubtful pathologic significance. The *P-R* interval was remarkably constant. In only 4 instances was there any example of delayed conduction. The *Q-R-S* complex showed a complete absence of any evidence of intraventricular block. The author concludes that "there is nothing to suggest the occurrence of gross cardiac lesions as a result of previous attacks of diphtheria," although he does point out that the abnormalities of the *T* wave in Lead III which are so common in active diphtheria have a tendency to persist long after the disease has subsided.

SURGERY

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Duodenal Drainage in Gall Bladder Disease.—About a decade ago there appeared a large number of papers dealing with the use of duodenal drainage in the diagnosis and treatment of disorders of the biliary tract. The interest in this subject was not prompted by new discoveries, but rather by the enthusiasm of individuals who attempted to correlate physiologic principles and clinical methods with diseases of the bile passages. The chief exponent of duodenal drainage for the diagnosis and treatment of disorders of the biliary tract was LYON (*Am. J. Med. Sci.*, 1920, 160, 515), who believed that by the application of the theory of MELTZER (*Ibid.*, 1917, 153, 469) concerning the contrary innervation of the gall bladder, and the sphincter of Gage and Oddi, the gall bladder could be made to empty its contents into the duodenum and that he could collect fractionated specimens of bile from the duodenum. From an examination of these bile fractions Lyon thought that he could differentiate various conditions of the gall bladder and by repeatedly draining the bile from the diseased gall bladder could restore that organ to its normal state. He not only felt that by this method he could determine the presence or absence of pathologic lesions of the biliary tract, but could localize the portion of the tract involved by the mucosal cells found in the material removed from the duodenum.

The objections which arose following Lyon's paper are too voluminous to include in a review. Suffice it to say that these objections dealt chiefly with the ability to cause emptying of the gall bladder, and even if the gall bladder could be made to empty, with the identification of the gall bladder fraction as such. In regard to treatment by duodenal drainage, those opposed to Lyon's method did not believe that it could bring about improvement in the presence of stones or in a viscus whose walls were infected. Unbounded enthusiasm on one hand and extreme skepticism on the other made it difficult to evaluate the

method. In 1924, JONES (*Arch. Int. Med.*, 1924, 34, 60) summarized the controversy thus: "Unquestionably, the early, rather extravagant claims for the method, as a means of diagnosis and treatment, have not been fulfilled. It is also unfortunately true that much of the criticism and pessimism with which the subject is now viewed is due to the claims that have been made by some enthusiasts as regards the efficacy of treatment by duodenal drainage. The undoubted psychologic effect produced by such treatment has undoubtedly been overlooked, or not mentioned by many. On the other hand, the somewhat unequivocal stand of Alvarez and other authors, that the method is without any value, seems equally unjustifiable."

When GRAHAM and COLE (*J. Am. Med. Assn.*, 1924, 82, 613) presented cholecystography as a means of determining the functional state of the gall bladder the question as to the efficacy of duodenal drainage was in doubt and the method was used routinely in but few clinics throughout the country. With the advent of cholecystography other tests for the diagnosis of disorders of the gall bladder became overshadowed. However, in spite of the widespread favorable results with the Graham-Cole test, there were those who, while not agreeing completely with Lyon, felt that the use of duodenal drainage had merit as a diagnostic test. LYON (*Am. J. Med. Sci.*, 1920, 160, 515) depended upon the color and consistency of the gall bladder fraction, the reaction, the microscopic appearance of the cellular debris, and the ease with which this dark fraction could be obtained, for his interpretation of the state of the gall bladder and bile ducts.

JONES (*Arch. Int. Med.*, 1924, 34, 60) and PIERSOL, BOCKUS and SHAY (*Am. J. Med. Sci.*, 1928, 175, 84) stated that a study of the sediment obtained after drainage was of the greatest diagnostic import, especially the finding of cholesterol or so-called calcium bilirubinate crystals. During the past year ROUSSELOT and BAUMAN (*J. Am. Med. Assn.*, 1933, 100, 254) and RAFSKY (*Am. J. Med. Sci.*, 1933, 185, 851) have published papers which emphasize anew the advantages of a study of this sediment in the diagnosis of cholelithiasis.

Whether or not the incidence of accurate diagnoses will be higher from a study of the crystallography of the bile obtained from duodenal drainage than from the more commonly used method of GRAHAM and COLE (*J. Am. Med. Assn.*, 1924, 82, 613) cannot be answered from a small series of cases presented from a few clinics. Either method of study requires skill not only in obtaining the necessary data, but in the interpretation of the findings. PIERSOL, BOCKUS and SHAY (*Am. J. Med. Sci.*, 1928, 175, 84), in comparing the two methods, reported correct diagnoses in 88 per cent of cases by means of duodenal drainage as compared with 65 per cent with oral cholecystography. Their results from duodenal drainage are very commendable, but the results from cholecystography seem low. Later, BOCKUS, SHAY, WILLARD and PESSEL (*J. Am. Med. Assn.*, 1931, 96, 311) in an additional study reported that in their hands duodenal drainage gave 98 per cent correct results as compared with 88.4 per cent by cholecystography. However, it appears that with individuals less skilled in duodenal drainage, cholecystography is still the method of choice for the diagnosis of gall bladder disorders.

Since much of the confusion concerning the place of duodenal drainage in the diagnosis of gall bladder disease has resulted from loose

terminology and much theorizing, the use of the term "calcium bilirubinate crystals" for the material which the adherents of the duodenal drainage method believe is characteristic of cholelithiasis is unfortunate, in that it suggests that the identity of the material is as well known as is the entity spoken of as "cholesterol crystals." The fact that this material is colored might suggest the presence of bilirubin, but there is no very plausible reason for stating definitely that the material is the calcium salt of bilirubin.

THERAPEUTICS

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The Treatment of Eclampsia and Pre-eclampsia With Thyroxin.—KÜSTNER (*Klin. Wchnschr.*, 1932, 11, 1016) and others claim that in eclampsia there is an increased activity of the hypophysis, with an increased production of posterior lobe hormone. Although evidence is available that thyroid function is also increased, as a result of the overactivity and antagonistic effect of the posterior lobe pituitary hormone, the balance is dominated by the latter. This concept suggests that the use of thyroxin in eclampsia is rational. The author administered thyroxin in 48 cases of eclampsia. The daily dose varied usually between 2 and 3 mg. by mouth. The total amount administered also showed considerable variations. One patient received 8 mg.; another, 48 mg. In 26 cases, the author claims an improvement due to thyroxin. The improvement manifested itself either in the cessation of convulsions or in decrease of the edema. In 18 cases the improvement was not definite. One patient died. None of the cases with marked improvement had an arterial pressure over 180 mm. Hg systolic pressure; but the edema in this group was usually of marked degree. The group with no improvement, on the other hand, exhibited a relatively higher systolic arterial pressure (180 to 230 mm. Hg) and slight edema only. Cases with pre-eclamptic manifestations showed particularly marked improvement. The author does not advocate thyroxin therapy alone, but states that in some cases it may be of great benefit. Even relatively large doses of thyroxin failed to exert obvious harmful effects on the mother or on the fetus.

Clinical Experiences With Glucose-insulin Treatment of Cardiac Disease.—Following the introduction of the therapeutic administration of glucose by Büdigen as a valuable addition to the usual methods of the treatment of cardiac failure, there has more recently been recommended a modification of his plan of therapy in which from 30 to 50 gm. of glucose are given orally or intravenously in the morning fasting state and are followed in from 15 to 20 minutes by a subcu-

taneous dose of 10 to 30 units of insulin. In view of the fact that insulin has been proved to exert harmful effects in the presence of the diseased heart, possibly because of its effect upon glycogen metabolism in the heart, LASCH (*Med. Klin.*, 1932, 28, 1675) studied this procedure in 12 patients suffering from the severest grade of chronic cardiac insufficiency. All 12 were subjected to thoroughly controlled observations which were continued over a considerable length of time. After their response to the prolonged administration of salt-poor diet, digitalis and salyrgan there was added without alteration in their previous treatment the daily administration for 10 days of 50 gm. of grape sugar administered orally and followed after 15 minutes by 10 units of insulin. The author was unable to find any evidence that this addition of sugar and insulin was in any way beneficial to the patient or altered his response to the previous treatment. In some of the cases, moreover, the patient's condition was actually less favorable following than before the administration of the sugar and insulin. The author concludes that this form of therapy for the decompensated cardiac patient is not only valueless but may actually be harmful. He specifically states, however, that this is not to be construed as reflecting upon the therapeutic value of the intravenous use of glucose without insulin.

Bichlorid of Mercury Inhalations in the Treatment of Gangrene of the Lung.—ENGEL (*Deutsch. med. Wchnschr.*, 1932, 58, 1924), having obtained such very satisfactory results from its employment along with other methods in the treatment of gangrene of the lung, seeks to reintroduce the use of inhalations of a vapor of a 1 to 1000 solution of corrosive sublimate. He reports 12 patients so treated in the last few years of whom 4 died, 3 were significantly improved and 5 completely cured. He administers these sublimate inhalations 2 or 3 times daily, spraying in the form of steam a dose of 25 cc. of the solution at each application. He has never seen any unpleasant or harmful effects in spite of sometimes having continued this treatment for 5 or 6 weeks, and there has never been any evidence of mercurial poisoning. He warns that on account of mild irritative conjunctivitis the eyes should be protected from the sublimate spray. The beneficial effects of the treatment usually begin promptly and are first seen in a diminution or disappearance of the putrid odor of the sputum and breath. This is followed by diminution in the amount of sputum and a fall in the temperature. Since the value of arsphenamin and of myrtol are so well established, he combines the administration of these agents with the use of sublimate spray.

Work and Insulin in the Management of Diabetic Patients.—It is established that in milder cases of diabetes moderate or severe muscular exercise usually acts beneficially; the blood sugar falls and the glycosuria may even disappear. In severe cases, on the other hand, there may follow an increased blood sugar content and glycosuria, and acetone bodies may appear. BRAUCH (*Deutsch. Arch. f. klin. Med.*, 1932, 174, 352) reinvestigated this problem with reference to the usual occupational work of the patient and to insulin dosage. For this purpose a comparison was made of the patients' behavior while performing their

usual work in the morning and while resting. These tests were repeated in some of the cases 2 months after the dietetic-insulin-work régime was established. In every case the arrangement followed has considered the individual occupation and character of the diabetes. The response of the patients to muscular work was not uniform. In 3 patients the occupational work resulted in a marked lowering of the blood sugar and urinary sugar elimination. In 7 patients a similar response was observed after moderate work. In 2 patients no difference was noted while at rest or while working. In 1 severe case the work resulted in an aggravation of the condition. The author emphasizes the value of individual gauging of work, diet and insulin.

PEDIATRICS

UNDER THE CHARGE OF
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Raw Basic Feeding in the Prevention and Treatment of Dental Caries.—KUGELMASS and KING (*Arch. Pediat.*, 1933, 50, 307) state that dental caries is a syndrome of many systemic and local disturbances rather than a simple disease of single etiology. Determination of the degree of dental caries was made by means of Bodecker's life caries index in children under continuous supervision for other systemic conditions. Children free from dental caries were of the more stable elements of their race, whose general and mouth hygiene were superior to children with marked dental caries. Dental caries is at its maximum at 6 years for deciduous teeth and at 12 years for permanent teeth, the incidence increasing rapidly with age. This rhythm parallels that of development, thus relating dental caries to deep-seated metabolic changes in the growing body. The degree and prevalence of dental caries was not affected by recurrent mouth and upper respiratory infections. Dental caries is neither prevented nor minimized by breast feeding. Children free from dental caries were maintained in infancy on base-forming dietaries containing early additions of semisolid feeding in the first months of life. Children with moderate and extreme dental caries showed inadequate intakes of vitamins B, C and D. Those maintained on ketogenic diets, base-forming in their mineral content, showed marked dental caries. Those free from dental caries showed consistently a dietary intake excessive in alkali-forming minerals with a preponderance of raw fruits and vegetables. Races immune to dental caries consume sufficient raw alkali-forming fruits and vegetables to balance the acid-forming fresh fish and raw meat.

The Relationship of the Rheumatic Process to the Development of Alterations in Tissues.—COBURN (*Am. J. Dis. Child.*, 1933, 45, 933) says that when the rheumatic subject is infected with the hemolytic streptococcus, the initial response is of the usual character. If the infection is limited to the upper respiratory tract, recovery follows in the course of a few days. This illness, although mild, may be the first

phase in the development of a severe rheumatic attack. Following the subsidence of the local infection, the patient usually regains his usual health, and nothing abnormal is detected clinically. This quiescent stage of days or a few weeks represents the second phase in the evolution of the rheumatic process. This second phase persists until there is a response in the production of immune bodies in the peripheral circulation, whereupon the rheumatic process is activated in susceptible persons. When this occurs, the initial response is characterized by manifestations of a hemorrhagic nature. The most frequent are epistaxis and the erythemas. Melena, hemoptysis and hematemesis also occur. Studies of the excretion of erythrocytes in the urine indicate that there is a very close relationship of hemorrhage to the rheumatic process. Late in the attack, when symptoms are subsiding and abnormal urinary manifestations have disappeared, there may be a second stage, characterized clinically perhaps only by the appearance of subcutaneous nodules. When it was possible to study the tissues of patients dying during the initial stage of a rheumatic attack, hemorrhagic lesions without distinctive histologic character were conspicuous. The appearance of these non-specific lesions suggested the activity of a single process with varying degrees of intensity. This varied from engorgement of the bloodvessels; alteration of the permeability of the vascular tissues with diapedesis, but without demonstrable change in the structure, to inflammatory reaction. The damage to the tissue in the patients with acute rheumatism was characterized by the absence of detectable microorganisms and commonly by vasodilatation, swelling of the endothelium, necrosis of the collagen, infiltration with various wandering cells, and especially hemorrhage. During the first cycle of the rheumatic attack, few or no Aschoff bodies were detected in the cardiac muscle, but the diagnosis was established by the presence of the specific lesions in the endocardium. In this group most of the rheumatic subjects who died survived a long illness with rheumatic fever. In these patients hemorrhage was not conspicuous, and numerous Aschoff bodies were found in the heart muscle. The constant proximity of the Aschoff cells to necrotic collagen in these myocardial nodules suggest the process of healing. The evolution of rheumatic fever consists of three phases. In most instances recognition of the condition clinically is not established until the development of the third phase.

Studies in Cretinism and Hypothyroidism: Blood Cholesterol.—BRONSTEIN (*J. Am. Med. Assn.*, 1933, 100, 1661) undertook this study in order to establish an additional method for regulating thyroid therapy, and so that the clinical course of the thyroid-deficient child might be better understood. It has been shown previously in adults that a relationship existed between hypercholesteremia and hypothyroidism. It was attempted to show that a similar relationship existed in childhood. The blood cholesterol was determined in 25 children in whom no known derangement of cholesterol metabolism was present, and the average was found to be 190+. This value for cholesterol is substantiated by the results of other investigators in this field. Hypercholesteremia was found in the 12 thyroid-deficient children studied. The values ranged from 277 to 782. Thyroid therapy definitely lowered

the blood cholesterol in the cases cited, in addition to raising the basal metabolic rate and effecting clinical improvement. It is desirable to have an additional method for the diagnosing and treating of thyroid-deficient children, particularly in infants and in borderline cases. The use of cholesterol as an aid in the diagnosis and the regulation of therapy offers very satisfactory and definite possibilities.

DERMATOLOGY AND SYPHILIS

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Bacteriologic Studies on Lichen Planus.—In a disease whose etiology has occasioned much speculation, JACOB and HELMBOLD (*Arch. Dermat. and Syph.*, 1933, 27, 472) present significant evidence for a specific organismal cause. These authors have isolated a Gram-negative, anaërobic, non-motile, non-spore-bearing bacillus from excised lesions in 25 of 28 cases of lichen planus studied. The organism, though somewhat polymorphic, resembles organisms of the colon typhoid type but cannot as yet be definitely classified because of its relatively poor growth. Semisolid dextrose serum agar containing cubes of human tissue was the medium used. The serum must be inactivated at from 56° to 60° C. for a number of hours. The organism was not found in normal skin nor in a number of cases of other papular diseases used as controls. Inoculation of human skin with the organism isolated in a few instances produced lesions which both clinically and histologically resembled lichen planus.

Postoperative Gangrenous Ulcer of the Abdominal Wall.—Increasing interest has been shown in the occasional development of post-operative gangrenous ulcers usually following septic operations on the abdominal cavity, generally in men, and DUEMLING and ELSTON (*Arch. Dermat. and Syph.*, 1933, 27, 624) give an excellent review of the literature, discuss the clinical features, and report an additional case following operation for a ruptured gastric ulcer, with new suggestions for treatment. While authorities vary as to the causative organism, the consensus of opinion points to a streptococcus and a staphylococcus which invades the tissues in symbiotic relationship. This type of progressive gangrenous ulceration usually develops about a drainage opening or stitch hole from 7 to 21 days postoperatively. Most cases follow operations on the gall bladder or intestinal tract in men, rare examples in women even after operation for pelvic inflammatory disease being on record, however. The condition begins as a small, painful, purplish papule which breaks down, ulcerates and spreads in a serpiginous

manner, involving skin, subcutaneous tissue and fascia. In the absence of effective treatment, the process will involve the entire abdominal wall within a period of a few weeks. The authors advocate the use of the infiltration of skin and subcutaneous tissue in advance of the gangrenous process with 5 cc. of bacteriophage (staphylococcus and colon bacillus). This was followed by a general reaction with chill and elevation of temperature to 103° F. in the patient under observation, but repetition of the infiltration at a 5-day interval for 3 times resulted in less systemic reaction and prevented further extension of the process. The authors also recommend the use of oxyquinolin sulphate and scarlet red impregnated gauze originally advocated by Bettman as an epithelial stimulant and for relief from pain attendant on changing dressings.

GYNECOLOGY AND OBSTETRICS

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Friedman Pregnancy Test.—Since the introduction of the Aschheim-Zondek biologic test for pregnancy, there has been considerable interest in work of this sort because of the very high percentage of accuracy. The modification of the test devised by Friedman, in which rabbits are used instead of mice, has been accepted by many investigators on account of certain economic and practical advantages. According to McNEILE and REYNOLDS (*Calif. and West. Med.*, 1933, 38, 1) the Friedman test has an accuracy of about 98 per cent, which parallels that of the Aschheim-Zondek test. It is as yet uncertain as to exactly how soon after conception the reaction becomes positive, probably not under 3 weeks, so that early pregnancy, if negative, should be checked a second time 7 to 10 days later. The test determines the presence of live placental tissue or tissue of placental origin in contact with the maternal circulation. It may, therefore, give false positives in the presence of missed abortions, incomplete abortions or ectopic pregnancies with dead fetal tissue. The reaction might be positive in the case of a macerated fetus as the placenta in these cases frequently contains live tissue. The test is strongly positive in the presence of hydatid mole and chorionepithelioma, and quantitative Aschheim-Zondek tests become an important aid in the diagnosis, treatment and prognosis of these conditions. Primary ovarian failure or castration may cause a compensatory hypertrophy of the anterior lobe of the pituitary gland which may throw an excess of its hormone into the circulation, thus accounting for a certain number of false positive reactions. The technique which they suggest is the injection of 7 cc. of fresh urine on 2 successive days, using a controlled rabbit over 12 weeks of age, killing the animal at 48 hours.

OPHTHALMOLOGY

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Ocular Syphilis.—III. Review of the Literature and Report of a Case of Acute Syphilitic Meningitis and Meningoencephalitis with Special Reference to Papilledema. DRAKE (*Arch. Ophthalm.*, 1933, 9, 234) reports a case of acute syphilitic meningitis and meningoencephalitis in which bilateral choked disks with concentric contraction of the visual fields and limitation of external and downward rotation of the left eye were prominent symptoms. The patient also had occipital headaches, rigidity of the neck, nausea and vomiting, left facial weakness and sluggish pupillary reactions. The Wassermann reactions of both blood and spinal fluid were strongly positive. The spinal fluid contained 227 lymphocytes per cubic millimeter. Under intensive antiluetic treatment, the edema of the disks receded promptly and had completely disappeared in about four months. The vision was considerably improved. Although some authorities believe that acute syphilitic meningitis is always a neurorecidive, only 11 of the 50 cases found in the literature by the authors had had previous antisymphilitic therapy. Of the 30 cases in which examination of the ocular fundus was recorded, 8 showed papillitis, 14 bilateral papilledema, and 2 unilateral papilledema. Argyll-Robertson pupils were present in 7 cases. The Wassermann reaction of the blood was strongly positive in 45 of 48 cases. The Wassermann reaction of the spinal fluid was strongly positive in 49 of the 50 cases. The average cellular content of the spinal fluid was 414 cells per cubic millimeter. The majority of the cells were lymphocytes. Papilledema of syphilitic origin is almost invariably a symptom of acute syphilitic meningitis or meningoencephalitis, which may occur during the secondary stage or more rarely as an acute exacerbation in congenital syphilis, or in a latent period of the tertiary stage. Associated symptoms are headache, nausea and vomiting, coma, delirium or some other mental disturbance, and involvement of other cranial nerves, especially the 3d, 6th, 7th and 8th. The Wassermann reaction of the blood is positive in about 90 per cent of cases, and that of the spinal fluid is always positive. The cerebrospinal fluid is always under increased pressure and contains an increased number of cells. If the Wassermann reaction of the spinal fluid is negative on several successive examinations, the diagnosis of acute syphilitic meningitis is not justified. The prognosis is usually good if antisymphilitic treatment is started promptly. The papilledema usually responds very well to antisymphilitic treatment, but in some cases is followed by postneuritic atrophy. Histologically, acute syphilitic meningitis is characterized primarily by a diffuse, small cell infiltration of the piaarachnoid in which lymphocytes predominate. The infiltration occurs especially around the bloodvessels and extends along them into the brain tissue. The region of the chiasm is often involved in the meningitic process, and the cranial nerves, especially the optic and auditory, are often markedly infiltrated with lymphocytes and plasma cells.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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The Relationship of Upper Respiratory and Alimentary Tract Flora to Mastoid Infections, With Particular Reference to the Epidemiology of Mastoiditis.—Wisely employing Holman's method for differentiating and classifying streptococci, KOPETZKY and HADJOPOULOS (*Laryngoscope*, 1933, 42, 661) correlate the bacteriologic findings of cultures made from otitic suppurative lesions with their analyses of certain statistics collected from the records of a general hospital during the sexennium 1926-1931. From an epidemiologic standpoint, it was found that approximately 3 per cent of the total hospital admissions were otologic cases, which seemed to increase in number triennially. The incidence of acute otitic infections reached the peak in March and April; whereas the greatest number of chronic cases occurred in August and September. The mortality curve virtually paralleled that of the chronic infections, and was highest when the general incidence was lowest. The authors believe their studies confirm a phenomenon common to all epidemics—namely, towards the end of the epidemic the ratio of mortality to morbidity shifts in favor of mortality. The general mortality rate was somewhat over 5 per cent, ranging between 8.6 per cent in 1930 and 2.3 per cent in 1931. Unable to explain this fluctuation satisfactorily by data at hand or by merely differentiating the streptococci (which were by far the commonest microorganisms encountered) into the three major groups—hemolytic, green and indifferent—the authors proceeded more minutely to analyze their bacteriologic data. The bacteriologic technique for differentiation and classification of the streptococci was that of Holman, although from the authors' description one gets the impression that the individual strains were not isolated in pure culture before being introduced into the differential fermentation "sets." Moreover, pneumococcus, Type III, is classified as a streptococcus. Hemolytic streptococci were found to be the infecting microbe in about 90 per cent of all cases. *S. pyogenes* accounted for 80 per cent of the cases dying from mastoiditis. *S. infrequens* was associated oftenest with chronic mastoiditis. Study of the annual variations of the streptococcic types in mastoiditis revealed an orderly sequential periodicity, suggesting major cyclic recurrences every 5 or 6 years. According to their findings, indifferent streptococci predominated in 1927 and 1929. *S. infrequens* in 1928, *S. pyogenes* in 1930, and *S. subscidus hemolyticus* in 1931. The authors state that "the existence of such a cyclic change in streptococcic types is borne out by the findings for all other metastatic foci as well as otitic infections." A related paper, "The Prognostic Value of Streptococcic Subculture in Affections of the Ear," was published subsequently by Hadjopoulos in *Laryngoscope*, 1932, 42, 771.

ABSTRACTOR'S NOTE.—Holman's original contribution, "The Classification of Streptococci," appeared in *J. Med. Res.*, 1916, 24, 377, and was abstracted in *AM. J. MED. SCI.*, 1917, 153, 427.

RADIOLOGY

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d'Arsonvalization in Hyperpiesis.—In the opinion of HUMPHRIS (*Arch. Phys. Ther., X-ray, Rad.*, 1932, 13, 786) the importance of the d'Arsonval current in its ability to lower a high blood pressure can hardly be overestimated. When there is failing ventricular compensation no attempt should be made to lower the peripheral resistance, but these cases are in the minority. In the great majority of cases the increased tension is due to the imperfect elastic recoil in the arterioles (even with arteriosclerosis) plus increased peripheral resistance, and in these cases the d'Arsonval current acts as a safe specific. The author regards it essential to employ apparatus capable of delivering 2500 ma. by the auto-condensation method.

A Roentgen Ray Sign in the Diagnosis of Reducible Esophageal Orifice Hernias.—A roentgenologic sign of reducible hernias at the esophageal orifice is described by CARTY (*Radiology*, 1933, 20, 174). The patient is examined in the vertical, right anterior oblique position, and the ordinary barium mixture is employed. While the breath is held in full inspiration the patient is told to swallow. At that moment the examiner exerts pressure on the anterior abdominal wall with his hand. If a hernia is present the barium stream usually takes an upward course as it is about to enter the stomach. For obvious reasons roentgenographic depiction is usually impracticable, and the observation is essentially roentgenoscopic.

What Do You Think of Physical Medicine?—SHAULL (*Arch. Phys. Ther., X-Ray, Rad.*, 1933, 14, 105) points out that it is as difficult to answer this frequently asked question as to answer "What do you think of Radiology?" or "What do you think of internal medicine?" Physical medicine is neither a cult nor a system of healing, and there is no definite line of demarcation between this specialty and surgery or internal medicine. To remove a tumor a surgeon may employ an ordinary scalpel, one heated in a bed of coals, one heated by an electric current, or a cold wire needle with an undamped high frequency current concentrated at its point. In the first two instances the procedures are recognized as surgical; in the last two the operator is perhaps employing physical therapy, although there is no vast difference between any of the methods. In a patient suffering from paresis the internist produces a certain number of temperature elevations by inoculating him with malaria. The physical therapist produces exactly the same number of temperature elevations of exactly the same curve

(if he elects) with diathermy or the hot bath. The results, as far as the paresis is concerned, are quite comparable. It is true that the internist has the malarial parasite and the anemia it has produced to deal with at the end of the series, while the physical therapist has only to turn off his machine or drain his tub. The attempt to evaluate physical medicine as a whole should be abandoned. It is almost as foolish as to attempt to evaluate internal medicine as a whole. In its place the critical evaluation of new appliances and methods of physical therapy by capable men is very badly needed.

NEUROLOGY AND PSYCHIATRY

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Psychologic Changes in Normal and Abnormal Individuals Under the Influence of Sodium Amytal.—LINDERMAN (Am. J. Psychiat., 1932, 11, 1083) feels that sodium amytal produces a marked change in the behavior of certain types of psychotic patients and a less pronounced change in the emotional attitudes of normal individuals, on the basis of the release of inhibitions. It allows the study of the thought content of stuporous patients, which was previously not possible and gives material which can be used in psychotherapeutic efforts.

Mental Disorders in Siblings.—HUMM (Am. J. Psychiat., 1932, 12, 239) presents a study of several hundred individuals in order to determine the relative importance of hereditary and environmental factors in persistent criminalism, manic-depressive psychoses, dementia precox, epilepsy and mental deficiency. The individuals consisted of 858 siblings of patients suffering from mental disorders and 214 pairs of twins, one or both of each pair being affected with a mutual disorder. He found that the closer the degree of genetic relationship to an affected subject, the greater the tendency to mental disorder; that some pre-natal factor or factors other than heredity play a part in the causation of mental deficiency; that such factor or factors are more frequently operative in twin than in single births; and that this factor or factors are apparently not operative in the other mental disorders studied. He found also that many siblings were affected with disorders dissimilar to those of their respective prepositi. He found a very frequent familial coexistence of epilepsy with migrainous headaches, enuresis and outbursts of rage. In a similar way he found a familial association between manic-depressive psychoses and cases of cycloid personality. The incidence of mutual disorder was greater in the males than in the females, although the female ratio is unquestionably greater in manic-depressive psychoses and in mental deficiency.

PATHOLOGY AND BACTERIOLOGY

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Contributions to the Pathologic Physiology of Inflammation: The Action of Histamin on Tissue Metabolism.—Experiments on white mice were carried out by BÜNGELER (*Frankf. Ztschr. f. Path.*, 1932, 44, 1) to determine whether histamin injected into the living animal or allowed to act directly upon fresh tissue *in vitro* would influence the tissue metabolism as determined by the Warburg method. It was shown that the injection of small amounts of histamin corresponding to about one-tenth of the lethal dose brought about a definite increase in the oxygen consumption of the liver tissue; the greatest increase was observed within an hour of the injection (40 to 50 per cent above the normal O_2 consumption) and fell off to normal within 2 or 3 hours. This type of increased metabolism corresponds to that observed by Hess (*Frankf. Ztschr. f. Path.*, 1931, 42, 89), following experimentally induced inflammation of the skin. The author, therefore, believes that the elevation of tissue metabolism observed by Hess was due to the liberation of histamin into the blood stream from the foci of inflammation in the skin. He draws attention to the evidence brought forward by other authors purporting to show the appearance of histamin in anaphylaxis and inflammation and concludes FISCHER-WASELS (*Frankf. Ztschr. f. Path.*, 1931, 42, 1) is correct in his theory that the toxic effects (*Fernwirkungen*) of inflammation are due in part at least to the liberation of products of protein disintegration, chief of which are histamin and allied substances. The injection of large doses of histamin leads on the other hand to a depression of liver metabolism (if the animal is examined in the stage of severe shock). This change of tissue respiration corresponds to that which the author has shown to occur in anaphylactic shock.

Contributions to the Pathologic Physiology of Inflammation: The Effects of Localized Inflammation on the Reticuloendothelial System as Determined by Vital Staining.—EICHBAUM and SCHEUFLEER (*Frankf. Ztschr. f. Path.*, 1932, 44, 10) produced extensive subcutaneous inflammation in rabbits by injections of silicious dust (*Kieselguhr*). They then investigated the ability of the reticuloendothelial system to take up vital dyes, and found that the absorption of trypan blue was mildly accelerated about 96 hours after the skin lesions were instigated. With Congo red they found no deviation from the normal. In contrast to the relatively slight effect produced on the reticuloendothelial system by localized inflammation, intravenous injection of milk gave rise to a conspicuous acceleration of the disappearance of Congo red from the blood stream. Subcutaneous injection of milk produced a similar but

more sluggish reaction. Intravenous injection of caseosan markedly accelerated the disappearance of trypan blue from the blood stream, but had no effect on the absorption of Congo red by the reticulo-endothelial system. The authors believe that the rapidity with which vital dyes quit the blood stream is proportional to the phagocytic activity of the reticuloendothelial system and feel justified in concluding that this function of the reticuloendothelial system is mildly increased as a result of localized inflammation, though the increase is small compared to that which can be produced by intravenous injections of foreign proteins.

On the Influence of the Vegetative System on the Cholesterin Content of the Blood.—The few observations made (*e. g.*, in cases of anaphylactic shock, pregnancy, dementia precox) on the influence of the autonomous nervous system on the proportion of cholesterin in the blood indicate that vagotony and hypercholesterinemia are associated with each other. GOEBEL (*J. de phys. et de path. gen.*, 1932, 30, 340) has studied the influence of the vegetative system on the level of cholesterin by pharmacologic methods. He uses a procedure based on the researches of Kraus and Zondek, increasing the quantity of calcium in the organism, and thus causing a temporary displacement of the equilibrium of the electrolytes in the blood in favor of calcium and obtaining excitement of the sympathetic nerve. Dogs were given intravenous administration of 0.2 grains CaCl_2 in 20 per cent solution per kg. weight, with determinations of the cholesterin in the blood before and at intervals after the injection. This showed that the raising of the tone of the sympathetic nerve by calcium salts brings about hypocholesterinemia. The predominance of the sympathetic nerve was then brought about by paralysis of the parasympathetic by strong doses of atropin (0.005 to 0.01 grains by kg. weight), and it was observed that within 1 hour after administration a diminution of the proportion of cholesterin in the blood was produced. Experiments were then made to study the behavior of cholesterin in the blood during tonic domination of the pneumogastric nerve. The vagus nerve was stimulated by potassium ions (KCl in 10 per cent solution) and then by paralysis of the sympathetic system with ergotamin (the "gynergene" preparation); hypercholesterinemia resulted. The author concludes that the production of cholesterin takes place in the suprarenals, ovaries and spleen, and that the straightening or weakening of the functions of these glands of internal secretion through the nervous system is the cause of the hypercholesterinemia or hypocholesterinemia in the subjects of the experiments.

Epithelial Repair in Recovery From Vitamin A Deficiency.—WOLBACH and HOWE (*J. Exp. Med.*, 1933, 57, 511) have studied minutely and recorded the process of repair of epithelium in recovery from vitamin A deficiency. In their opinion absence of vitamin A causes a starvation specific for many epitheliums. This results in an atrophy and finally in the formation of a stratified keratinizing epithelium regardless of the morphology of the original epithelium. As had been shown previously, this metaplasia is the earliest demonstrable effect of vitamin A deficiency in rats. They found that correcting the vitamin A defi-

ciency in the diet before metaplasia was complete resulted in a rapid restoration of an epithelium identical in morphology with the original epithelium, before the deficiency diet was instituted. In rats in which the process of metaplasia was completed, by keeping the animals on a diet deficient in A for a suitable length of time, they found the process of repair to consist of a vascular degeneration of cells, the upper stratum disappearing by lysis while the lower stratum developed into cells normal for that location. Permanent loss of identity of an epithelium may occur where infection has occurred in cysts or in cases of cicatrized glands. The authors conclude that since the cells of the stratum germinativum preserve the identity of the original epithelium, that this identity is contained within the nuclear chromatin, which is, therefore, unaffected by the deficiency. It is noteworthy that the authors' series of rats were remarkably free of infection, and this gives support to the statement that the condition of vitamin A deficiency does not increase susceptibility to infection by bacteria.

HYGIENE AND PUBLIC HEALTH

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A Study of Tuberculosis Among the Indians in Montana.—CROUCH (*U. S. Pub. Health Rep.*, 1930, 47, 1907) states that in Montana the death rate from tuberculosis among the Indians is about 15 times as high as among the whites. Among mixed bloods the tuberculosis death rate is much lower than among full-blood Indians. When tuberculin-tested (Mantoux) the figures for positives among children was as follows: Full-blood, 75 per cent; mixed blood, $\frac{1}{4}$ and more Indian, 54.3 per cent; mixed blood, less than $\frac{1}{4}$ Indian, 39.3 per cent; whites, 22.6 per cent. Furthermore, it was shown that above the age of 17 years all full-blood Indians tested were positive, while mixed-bloods showed lower figures of positives than in earlier years. The question of race susceptibility is not settled, but it is suggested that complete healing is less frequent in full-blood Indians.

The Preparation of a Vaccine From Fleas Infected With Endemic Typhus.—DYER, WORKMAN, RUMREICH and BADGER (*U. S. Pub. Health Rep.*, 1932, 47, 1329) review the preceding work on typhus and Rocky Mountain spotted fever and record the results of their own experiments. Fleas of the species *X. cheopis* infected by feeding on white rats were emulsified and the potency of the emulsion tested on guinea pigs. The virus then was destroyed by the addition of phenol

and used to inoculate guinea pigs. Some protection was shown when the immunized animals were later inoculated with living typhus virus together with a suitable number of control animals.

Duration of Viability and Virulence of *Bacillus Pestis*.—FRANCIS (*U. S. Pub. Health Rep.*, 1932, 47, 1287) subjected a single strain of *B. pestis* to 4 tests of duration of viability and virulence. Pure, undiluted, neutral glycerin at -15°C . was used for suspending the spleen of a plague guinea pig in one test, while a pure culture of *B. pestis* isolated from the same guinea pig was suspended in glycerin at -15°C . in another test. The bacilli in the spleen were viable and fully virulent at the end of 7 years, while the glycerinated pure culture was fully virulent for 14 months, slightly virulent for 2 years, 7 months, and dead at the end of 3 years, 5 months. A plain agar culture of *B. pestis* was stored at 10°C ., sealed and unopened, for nine years in 1 test, while in another test a plain agar culture was subcultured every 3 months for 9 years along with other cultures in a general collection of stock cultures stored at 10°C . The result at the end of 9 years was viability and full virulence of the sealed culture, but viability and nonvirulence of the stock culture.

The Social Incidence of Rheumatic Heart Disease. A Statistical Study in Yale University Students.—PAUL and LEDDY (*AM. J. MED. SCI.*, 1932, 184, 597) found the incidence of rheumatic heart disease in a group of 7914 undergraduate students of Yale University to be 8.2 per 1000, as compared with 15 per 1000 which is an average figure obtained from statistics of comparable age groups of individuals in other walks of life. Among the men in this group who had attended expensive boarding schools the incidence was only 5.8 per 1000 as compared with 12.5 per 1000 among those from high-schools. The contention that rheumatic fever is a disease which finds a lower incidence among people of ample means finds support in these observations. According to the methods employed the factor of poverty does not, however, seem to be as important a predisposing rôle in determining the incidence of rheumatic heart disease as it does in clinical tuberculosis.

The Prevention of Rickets.—MITCHELL and COLEY (*J. Am. Med. Assn.*, 1932, 99, 1768) conclude from their studies of a group of 139 babies over a period of 2 years that either cod-liver oil, in doses of 2 or 3 teaspoonfuls daily, or viosterol, in doses of 8 or 10 drops daily, exert a definite influence against the development of rickets, and by either treatment severe or even moderately marked rickets is prevented in babies who live in good hygienic surroundings. In spite of the aforementioned therapy, 22.3 per cent of patients show clinically mild rickets. In 15.9 per cent of the cases the Roentgen findings were positive. The administration of cod-liver oil in the dosage mentioned completely protects 82 per cent of the patients, while the given dose of viosterol completely protects only 75 per cent, in spite of the fact that the amount of viosterol has a little more than twice the amount of vitamin D contained in the daily dose of cod-liver oil. The lowest prevalence of rickets, 9.9 per cent, occurred among those given sunbaths in summer and viosterol or cod-liver oil in winter. The ultra-

violet ray is a satisfactory substitute for sunbaths, the incidence of rickets in those so treated being 13.6 per cent. In the causation of rickets there must be other factors than a deficiency of vitamin D—a comparative deficiency of vitamin A as expressed by De Sanctis and Craig, a deficiency of minerals in the diet as suggested by Weston, or perhaps some other as yet unrecognized agent in which the influence of light possibly plays as important a part as it does in the activation of ergosterol.

Oysters and Anemia.—COULSON, LEVINE and REMINGTON (*Am. J. Pub. Health*, 1932, 22, 1141) report results to show that the oyster is equalled or excelled only by liver in the amounts of iron and copper which it may furnish to the diet in an average serving. That these metals are easily available for hemoglobin production has been shown in previous work in which it was found that oysters, oyster ash (acid soluble) and a solution of iron, copper and manganese in the same quantities, fed to anemic rats, brought about hemoglobin regeneration at the same rate in all 3 cases. Oysters should, therefore, be efficacious in the treatment or prevention of those types of secondary anemia which respond to treatment with iron, or iron plus copper. There is increasing support for the view that dietary deficiencies can best be corrected by proper selection of foods, rather than by the use of artificial concentrates or medicinal mixtures. In order to insure an adequate supply of the inorganic constituents for hemoglobin production it would seem a wise plan also to include oysters in the diet of the pernicious anemia patient in conjunction with liver extract, since it is known that liver extract is relatively low in iron. An average serving of oysters (110 gm.) would furnish about 2 per cent of the human calorie requirement (3000 calories), and yield about 40 per cent of the daily dietary standard for iron, stated by Sherman to be about 15 mg.

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ORIGINAL ARTICLES.

ACETYL- β -METHYLCHOLIN.

I. THE ACTION ON NORMAL PERSONS.

WITH A NOTE ON THE ACTION OF THE ETHYL ETHER OF
 β -METHYLCHOLIN.

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Introduction. In a recent study conducted in this laboratory, André Simonart¹ made a survey of the physiologic actions of a number of compounds of cholin, some of them new, synthesized for him by R. T. Major and his colleagues² in the Laboratories of Pure Research of Merck and Company. The work was undertaken because the cholin group contains a number of highly active compounds and because of the unique interest which one of these, acetyl cholin, has come to possess. First discovered as a product of artificial synthesis, acetyl cholin was later found to be present in ergot and more recently, in fresh animal tissue. Its physiologic

activity is very great, being of an order similar to that of adrenalin or histamin. Among its conspicuous actions are inhibition of the heart and increase in intestinal movement. Dale³ has shown that there are good reasons for believing that when the vagus nerve to the heart and intestines is stimulated, acetyl cholin is released in the corresponding muscle cells and that the response induced is actually effected by the action of this chemical substance. With respect to these aspects of its action, therefore, acetyl cholin may be regarded as a chemical intermediary between parasympathetic nerve stimulation and muscular response.

The two features in the action mentioned above are among those designated as "muscarin-action" or parasympathetic action. Both are abolished by atropin. Another feature of the action, also abolished by atropin, is even more conspicuous, viz.: its power to cause dilatation of small arterioles and hence to lower blood pressure. This dilator effect is exerted not only upon vessels which possess parasympathetic innervation (*e. g.*, the submaxillary gland) but also upon those which do not (*e. g.*, vessels of the limbs). But Dale has pointed out that in these instances also there is ground for believing that stimulation of their dilator nerves (chorda tympani and posterior root fibers) is followed by the release of a chemical substance which is responsible for the consequent vasodilatation, and that this substance is acetyl cholin. If his views, based on an impressive mass of evidence,* are accepted we are obliged to regard acetyl cholin as an endogenous pharmacologic agent, released at need within the body, for the purpose of mediating highly important circulatory and gastro-intestinal reactions to nerve stimulation.

A third aspect of the action of acetyl cholin is commonly referred to as its "nicotin-action." Less conspicuous than the others, its most important feature is seen when acetyl cholin is injected intravenously into an animal after a preliminary dose of atropin. A marked rise of blood pressure ensues due to stimulation of sympathetic ganglia. When small doses are given without atropin this effect does not appear, being masked by the predominant peripheral dilator action.

Acetyl cholin is rapidly hydrolyzed in blood with the production of the far less active cholin. In consequence, no action results from oral administration; only slight and inconstant effects follow subcutaneous injection, and the actions of which we have spoken above, elicited by intravenous injection, are exceedingly evanescent. Knowledge of this instability and of its comparative ineffectiveness when given to normal man supply reasons for doubting its usefulness in human medicine.⁴

Other compounds of cholin are known which possess in different degrees the physiologic characteristics of acetyl cholin. It seemed

* The voluminous literature concerning cholin and acetyl cholin has been reviewed in Dale's Croonian lecture³ and the references to it may be obtained from this.

not unreasonable to expect that some of these or others yet to be made might be less readily hydrolyzed, might exhibit accentuated parasympathetic effects in relation to the nicotin effects, and hence might possess greater promise as drugs potentially useful in the treatment of disorders characterized by diminished parasympathetic or by excessive sympathetic tone. Simonart's work was based upon this thought and unique opportunity for testing it was afforded by collaboration with Major and his colleagues who shortly before had discovered new chemical methods for synthesizing cholin compounds.

Two substances were encountered which, partially at least, realize the expectations with which the work was begun. These are acetyl- β -methylcholin chlorid $(\text{CH}_3)_3\text{N}(\text{Cl}) \text{CH}_2\text{CH}(\text{CH}_3) \text{COOCH}_3$, and β -methylcholin chlorid ethyl ether $(\text{CH}_3)_3\text{N}(\text{Cl}) \text{CH}_2\text{CH}(\text{CH}_3) \text{OC}_2\text{H}_5$. Their actions have therefore been subjected to more detailed study than Simonart was able to give them, both in animals⁵ and in man, and the former has been used with encouraging results in the clinic. The present paper deals with effects produced in normal men. In a second, a study of the gastro-intestinal action in normal and diseased conditions will be presented. Experience with the drugs in the treatment of cardiovascular disease forms the subject of a third communication and a general resumé of the therapeutic possibilities has been appended to this.†

I. Action on Normal Persons. Acetyl- β -Methylcholin. A brief description of the actions of this substance in animals was published by Reid Hunt⁶ in 1914. Simonart's results do not agree with his and reasons were found for believing that the material used by Hunt consisted of mixtures of derivatives of α and β methylcholins. According to Simonart acetyl- β -methylcholin chlorid is much less readily hydrolyzed by blood than is acetyl cholin,⁷ possesses marked muscarin and peripheral vasodilator actions and exhibits little if any of the nicotin action of acetyl cholin.¹ More detailed study of its effects in animals has been made by Comroe and Starr.⁵

Crystals of acetyl- β -methylcholin chlorid are so hygroscopic that the substance cannot conveniently be given in any dry form. It is freely soluble in water and its watery solutions do not deteriorate on standing and are relatively stable to heat. They have a bitter taste. For subcutaneous administration we have used a solution containing 20 mg. to the cc., sterilized by boiling. This caused no discomfort at the site of injection.

Effects After Subcutaneous Injection. Twenty healthy medical students served as volunteer subjects. The routine observations were made by ourselves or by students supervised by one of us. Each subject lay on a couch during the time of the experiment; this included a preliminary control period of 15 minutes or longer. Dosages ranged from 2.5 to 25 mg.

† We are indebted to Merck & Co. for supplying the cholin compounds used in these investigations.

A typical effect after a dose of 20 mg. is shown in Fig. 1 and the signs and symptoms occurring after the various doses are summarized in Table 1. The action appeared within a minute after the injection. Flushing of the face and neck, generalized sweating, salivation, slight fall of blood pressure, increased depth of respiration during this fall, and increase in pulse rate were almost constant features. The effect on blood pressure passed off within a few minutes. The rapid pulse rate was also transient and was often

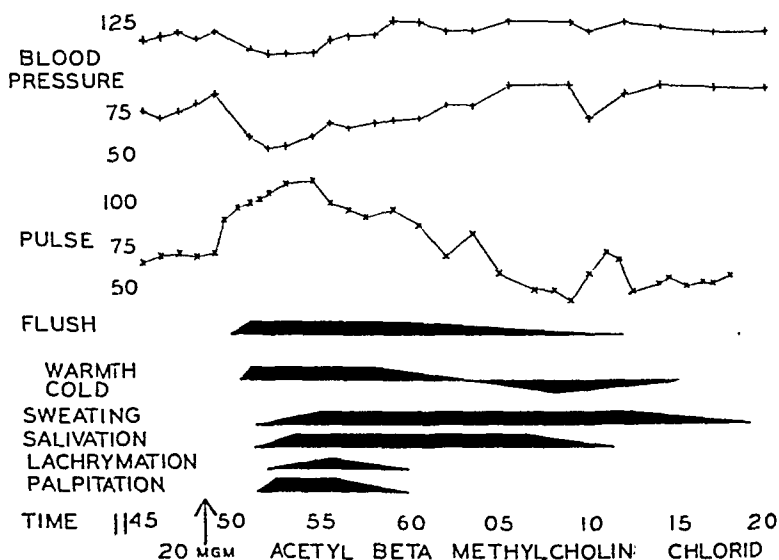


FIG. 1—Action after subcutaneous injection.

followed by a rate slower than that present in the control period. The other effects persisted for several minutes longer. The subjects, who felt warm during the flush, complained of chilliness after it had disappeared. They were glad to continue to lie down until complete recovery was attained in 15 or 20 minutes.

We listened to the hearts of many subjects during the action of the drug. When the heart rate was slowed sinus arrhythmia appeared in most of the cases. It disappeared as the action of the drug passed off. No other type of cardiac arrhythmia was encountered. Nothing else of importance was heard. One subject was connected to the electrocardiograph (Lead II) and records were made at frequent intervals before and during the action of the drug. Besides the effect on the heart rate no significant changes were demonstrated.

We obtained no evidence of dilatation of the vessels of the extremities after subcutaneous administration. The flush was confined to the area of the emotional blush. The right foot of two subjects was placed in a Stewart calorimeter.⁸ No increase in the output of heat by the foot was detected during the action of the drug.

The action on the secretion of sweat and saliva was very pronounced. In most subjects the underclothing became dampened. Salivation was also very marked. One subject who before the injection could expectorate only 0.5 cc. of saliva per minute, expectorated 4 cc. per minute during the drug's action.

TABLE 1.—EFFECT OF THE ADMINISTRATION OF ACETYL- β -METHYLCHOLIN SUBCUTANEOUSLY AND BY MOUTH TO NORMAL PERSONS.

	Subcutaneous dosage.				Dosage by mouth.					
	5-9 mg.	10-19 mg.	20-29 mg.	50-80 mg.	100 mg.	200 mg.	300 mg.	400 mg.	500 mg.	1000 mg.
No. of cases in each group	8	5	7	5	5	5	4	1	1	6
No. of cases showing effects given below										
Systolic B. P. mm. Hg.										
No change	3	1	1	2
Fall less than 10	1	2	1	2	1	1	1
Fall 10-20	3	4	3	3	1	2	2	1	1	1
Fall more than 20	1	..	1	1	1	1
Rise	1	..	1	..	1	1	1
Pulse rate per min.										
No change	1	3	2	2
Increase less than 10	1	1	..	1	1
Increase 10-20	1	1
Increase more than 20	6	5	7
Decrease under 10	1	1	2	2	..	3	1
Decrease 10-20	2	1	..	3	1	..	3
Flush	8	5	7	1	..	2	2	5
Early sensation of warmth	6	5	7	2	1	3
Later sensation of cold	3	1	3	1
Sweating	5	5	7	2	1	1	1	..	1	4
Salivation	5	5	7	1	1	1	2
Lachrymation	3	2	3
Increased peristalsis	2	..	2	1	..	1	1	5
Epigastric discomfort	1	1	2	2	..	1	..	2
Constriction under sternum	1	..	1
Palpitation	8	5	7
Increased respiration	8	5	7

Aside from the transient increase in depth of breathing no effects of the drug on the respiratory system could be demonstrated in the majority of our subjects. We listened to the chests of 5 subjects but could not detect râles in any. Three others coughed a few times.

One subject had a typical asthmatic attack immediately following the administration of the drug. It lasted for about 3 minutes and then subsided spontaneously. This was the only reaction to the drug which could be considered at all alarming. The subject gave a history of having had asthma before, and the attack can be attributed to the bronchoconstrictor action of the drug, which has been demonstrated in animal experiments.⁵ Three other subjects reported a sensation of "pressure" or "constriction" under the sternum, and one referred this sensation to the precordium. The cause of these sensations may only be surmised; perhaps they should be attributed to bronchoconstriction.

Gastro-intestinal effects were demonstrated in only a few subjects. We listened for peristalsis in 5 subjects before and after

the administration of the drug. An increase in frequency and intensity of the sounds was very obvious in 2; in the others this was not obvious, possibly because peristalsis was very active before the drug was given. Four others reported that they had increased bowel movements during the subsequent 6 hours. One of these had 3 liquid stools. One subject reported slight nausea after the injection; it passed off quickly.

In 2 subjects we were unable to demonstrate any effect on either the basal metabolic rate, the respiratory quotient, or the blood sugar after injections of 5 and 15 mg.

The Action After Administration by Mouth. The promptness and severity of the symptoms which followed the subcutaneous administration of acetyl- β -methylcholin chlorid stand in sharp contrast with the slow onset and mildness of the action after giving the drug by mouth. The dosage required to produce noteworthy effect by mouth was between 50 and 100 times as large as the subcutaneous dosage. Even after the largest doses the effects came on so gradually that the subject was usually entirely unaware that the drug was acting.

The action after administration by mouth has been studied in 27 subjects, 14 of whom were normal medical students or members of the staff, the remainder being hospital patients who were essentially normal. The majority of the observations were made on subjects who remained lying down for the whole morning. A few continued to perform their duties around the hospital ward and sat in a chair for 10 minutes prior to the taking of observations.

A summary of the effects detected after various doses of acetyl- β -methylcholin chlorid is given in Table 1. The initial effects were noted from 15 to 75 minutes after the administration of the drug. The duration of the symptoms depended on the dosage. After small doses they usually continued for $\frac{1}{2}$ to 1 hour; after the largest doses they lasted much longer, for 3 hours in 1 subject. The typical effects were a fall in blood pressure, the diastolic often falling farther than the systolic, and a diminished pulse rate. After small doses the other symptoms which occurred so regularly after subcutaneous injections were usually absent, after large doses they usually appeared as shown in Table 1.

The gastro-intestinal action usually exceeded that demonstrated after subcutaneous injection. Increased peristalsis was regularly noticed by the subjects and audible to the observer after doses of 1 gm. Defecation did not always follow because in 5 of the 6 subjects taking this dose the action was cut short by atropin. The 1 given no atropin had 3 bowel movements. Another subject had the same number after taking 50 mg.; 2 others had single stools.

Eight of the subjects complained of slight epigastric discomfort immediately after taking the drug, long before any other action was demonstrable. This was not true nausea and there was no

fear of vomiting. We later learned that this could usually be avoided by giving the drug in milk, so the discomfort is to be attributed to local irritation.

As the flush, so obvious in the face and neck, could not be seen elsewhere, 5 experiments were made to determine whether any vasodilatation occurred in the feet. The subjects lay on a couch with their feet bare. Thermal junctions were fastened to the dorsum of each second toe by wide strips of adhesive, and the skin temperature was determined at frequent intervals before and during the action of 1 gm. acetyl- β -methylcholin chlorid, given by mouth, and after 0.6 mg. of atropin sulphate had been given subcutaneously to antagonize its action. During the control period the skin temperature always diminished steadily toward that of the room air. In 3 instances, when the other symptoms of the drug's action commenced, the skin temperature stopped falling and began to rise. In 1 case the increase amounted to 4° C and was accompanied by some reddening, in the other 2 it was much less, 0.7° C., and no change of color was detected. As the room temperature did not change, the blood pressure did not rise and sweating increased during the drug's action, the increased skin temperature may be interpreted as indicating vasodilatation. This effect was halted by atropin in 2 of the 3 subjects. In 2 subjects no evidence of a vasodilator action on the feet was secured.

In 2 subjects (S. and C.) the effects of the drug on respiration and cardiac output were studied by means of the method of Starr and Gamble.⁹ The subjects had had no food for 15 hours and they rested 1½ hours before the first estimation and remained lying down throughout the determinations. Duplicate estimations were made before the drug was administered, a second pair after characteristic changes in blood pressure and pulse rate had taken place, a third pair after the action had been antagonized by atropin. Dosages of 200 and 400 mg. produced no noteworthy change in respiration or cardiac output in these cases, nor did any change follow the administration of atropin.

In these same experiments the metabolism was estimated from samples of expired air taken from the mixing bottle; in 2 other subjects it was determined by the Benedict-Roth apparatus. We are indebted to Dr. Robert Shaw for the analyses of the samples. In 2 instances the metabolism was unaltered; in 2 others it fell considerably. As 1 of the latter subjects had shown no metabolic change after a subcutaneous injection, the diminution is not to be attributed to the drug.

An electrocardiogram was taken after a dose of 100 mg. by mouth had caused a slowing of the heart rate to less than 60 a minute. It demonstrated a simple bradycardia with sinus arrhythmia. Another electrocardiogram taken on the same subject after the effect of the drug had passed off did not show sinus arrhythmia.

One subject, a strong and vigorous man, took a gram of the drug 4 times a day for 2 periods totaling 35 days. During the first few days of each period the laxative action was marked; the patient's stools increasing from 1 to 3 or 4 daily. This continued for several days and then the number of stools slowly diminished to normal, though the drug was continued. Salivation was noted at irregular intervals occurring 15 to 25 minutes following the taking of the drug. Increased sweating was not observed by the patient, but the test was conducted in mid-summer and some sweating was usually present. The night and morning pulse rates were not significantly different during the administration of the drug from those obtained before and afterward. The blood pressure was irregular during the control periods and there was no noteworthy change during the action of the drug. The subject had no discomfort at any time.

Other Methods of Administration. The intramuscular injection of acetyl- β -methylcholin chlorid into 2 normal medical students produced effects which seemed identical with those obtained after subcutaneous administration. When a solution of the drug was sprayed on the mucous membrane of the nose a definite flush of the face was observed in 2 cases.

Intravenous administration has not been attempted in man. The rapidity and vigor of the effects following subcutaneous administration indicate that the action following intravenous injection would be very severe. Judging from animal experiments, prolonged cardiac arrest would follow an overdose.

Comparison with and Relation to the Action of Other Drugs. The power of atropin to abolish the action of acetyl- β -methylcholin chlorid was demonstrated many times on our subjects. If 0.6 mg. of atropin sulphate was given subcutaneously an hour before an injection of the acetyl- β -methylcholin chlorid the latter had practically no effect, very transient flushing being the only thing observed. When this dose of atropin was given in the same solution as the acetyl- β -methylcholin chlorid, the action of the latter appeared with the usual intensity, but its duration was considerably shortened. If the same dose of atropin was injected when the action of a previous injection of acetyl- β -methylcholin chlorid was at its height, it caused a material shortening of the duration of the action.

It is of interest to compare the action of acetyl- β -methylcholin chlorid with that of acetyl cholin. The latter drug was injected subcutaneously in doses of 50, 70 and 100 mg. into 6 subjects, who also received acetyl- β -methylcholin chlorid. Acetyl cholin had very little effect even in the largest dosage, the blood pressure and pulse rate rising a little, but not more than is likely to occur from apprehension in this type of experiment. Several subjects objected to the pain caused at the site of injection. In 2 slight transient flushing occurred. We regard this as the only definite evidence we

obtained that this drug was acting at all. The effect was much less than that regularly obtained after a subcutaneous dose of 5 mg. of acetyl- β -methylcholin chlorid. Therefore, there can be no doubt that acetyl- β -methylcholin chlorid is a much more powerful and more dependable drug than acetyl cholin when administered subcutaneously in man. Even after intravenous injection the action of acetyl cholin seems too transient for therapeutic usefulness.⁴

THE ETHYL ETHER OF β -METHYLCHOLIN. The ethers of cholin are more stable than the esters, and so they might be superior for oral administration. This afforded the reason for making some preliminary experiments on the action of the ethyl ether of β -methylcholin chlorid which is known to be more stable in body fluids⁷ than acetyl- β -methylcholin chlorid although it is somewhat less active.⁵

Subcutaneous doses of 10 or 20 mg. of this drug given in aqueous solution (1 cc. = 20 mg.) to 5 normal persons produced effects similar to those described for the same doses of acetyl- β -methylcholin chlorid except that the action on blood pressure and pulse rate was less marked, while that on the secretion of sweat and saliva was of longer duration than the effects obtained after acetyl- β -methylcholin chlorid.

When given by mouth the effective dose of the ethyl ether of β -methylcholin chlorid was found to be considerably smaller than that of acetyl- β -methylcholin chlorid, ranging from 20 to 100 mg. It has been given to 10 normal persons. The typical response to such dosage was very marked sweating and very marked salivation, which lasted from 30 to 90 minutes. There was comparatively little change of pulse rate or blood pressure. However, the circulatory effects, as flush, diminution of blood pressure and pulse rate, were observed in some cases. The laxative action was seen in 2 cases. It, therefore, appears that the ethyl ether of β -methylcholin chlorid is the better drug for the production of sweating or to increase the flow of saliva, but if effects on the cardiovascular system are desired, acetyl- β -methylcholin chlorid is superior.

Summary and Discussion. In experiments on 47 normal persons, acetyl- β -methylcholin chlorid has proved to be a drug which, when injected subcutaneously in suitable dosage, exerts a prompt and vigorous action. A fall in blood pressure, a rise of pulse rate, flushing, sweating and salivation are the outstanding effects. The acute phase of this action comes on within a minute or 2 after injection and lasts for 2 or 3 minutes. All evidence of action passes away in 15 or 20 minutes. The only untoward effect encountered was the production of a transient attack of asthma in a subject who had previously suffered from this condition.

Given by mouth, acetyl- β -methylcholin chlorid has a much milder effect than that following subcutaneous injections. Given by the former method, even in very large doses, it does not cause discom-

fort, although considerable blood pressure and pulse rate changes have been noted. The dosage required to produce effects by mouth is so much larger than the subcutaneous that the destruction of large amounts of the drug in the gastro-intestinal tract seems probable.

The ethyl ether of β -methylcholin given by mouth or subcutaneously has less effect on the cardiovascular and gastro-intestinal systems, but more effect on the salivary and sweat glands than acetyl- β -methylcholin chlorid. Therefore, the latter seems preferable in all cases except where sweating and salivation are especially desired. That the ethyl ether of β -methylcholin chlorid is a vigorous diaphoretic without many untoward side effects is undoubted.

Most of the effects of these drugs demonstrated in man are similar to those obtained in animal experiments.^{1,5} They are analogous to those which follow stimulation of the parasympathetic nerves accompanied by peripheral vasodilatation. An exception to this statement is the increase of pulse rate which occurred so regularly in our subjects after a subcutaneous injection of the drug. Light is thrown on this apparent contradiction by a number of observations. In a few subjects, after large doses of the drug, we have demonstrated a sharp fall in pulse rate before the flush began and the blood pressure diminished. This fall lasted only a few seconds and was then succeeded by the characteristic rise. In many subjects, as illustrated in Fig. 1, after the acute phase of the action was over, the pulse rate diminished until it was slower than before the drug was administered. In 1 case, during this period of slowing, a subcutaneous injection of atropin sulphate in sufficient dosage to abolish the action of acetyl- β -methylcholin chlorid was followed by an increase of 10 beats per minute. This indicated that the slowing was due to the drug. As this decrease of heart rate occurred before and after, but not during the period of diminished blood pressure, it seems likely that the compensatory mechanisms which are called forth by any sharp fall of blood pressure, caused the heart to break away from the vagus inhibition. After administration by mouth the blood pressure falls so slowly that this type of compensation is not needed, and slowing of the pulse is the usual finding.

It is of interest to compare the action of acetyl- β -methylcholin chlorid with that of acetyl cholin in our normal subjects. In animal experiments an intravenous injection of acetyl- β -methylcholin chlorid has effects on the cardiovascular system essentially similar to those which follow acetyl cholin.¹ But judging by the effects which follow subcutaneous injections into normal men, acetyl- β -methylcholin chlorid is over 10 times as powerful. It can also be given by mouth whereas acetyl cholin is ineffective when thus administered. It also lacks certain of the undesirable side effects of acetyl cholin. Therefore, we believe that acetyl- β -methylcholin should supplant acetyl cholin in all conditions in which that drug is used for therapeutic purposes.

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ACETYL- β -METHYLCHOLIN.

II. THE ACTION ON THE GASTRO-INTESTINAL TRACT OF NORMAL PERSONS, IN ABDOMINAL DISTENTION, AND IN CERTAIN OTHER CONDITIONS.

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ALLUSION has been made in the first paper¹ of this series to the probability that in the normal animal stimulation of the vagus nerve to the gastro-intestinal tract is followed by increased motor activity because of the liberation in the muscle cells of the highly active chemical substance acetyl cholin. This conception was in part derived from the results of experiments conducted in Magnus' laboratory² which suggested that cholin was of importance in the regulation of normal gastro-intestinal motility. The instability of acetyl cholin in blood, responsible we believe for absence of action when given by mouth, and for inconstant effects when given subcutaneously, makes it of little importance as a drug. When it was discovered that acetyl- β -methylcholin is more stable than acetyl cholin,^{1,3,4} that it possesses similar parasympathetic actions, that in animal experiments it is highly effective in increasing the contractions of gastro-intestinal muscle and that it frequently exhibits laxative action when given to normal men, it became apparent that its possibilities as a useful drug should be studied in the gastro-intestinal clinic. The results of such a study are reported in this paper.

METHODS. *Gastric Secretion.* For study of the effect of the drug on gastric acidity, the entire contents were withdrawn as completely as possible at intervals varying from 5 to 20 minutes through a small stomach tube. Ten cc. of each specimen were used for analysis; the rest was returned to the stomach. Acidity was determined by titration with N/50 NaOH, using dimethylaminoazobenzene and phenolphthalein as indicators.

Gastric Tone and Peristalsis. The subjects swallowed a rubber balloon attached to a stomach tube. The balloon was then filled with 100 cc. of water and the tube connected with a tambour for recording gastric contractions. A levelling bulb was used for keeping the pressure on the contents of the balloon constant at about 15 cm. of water (Fig. 1). This procedure was frequently carried on coincidentally with the colonic studies noted below.

Tone and Peristalsis of the Jejunum were similarly recorded by the use of a smaller balloon carried into the jejunum by normal peristalsis. It was filled with 30 cc. of water, and its position was determined by the fluoroscope.

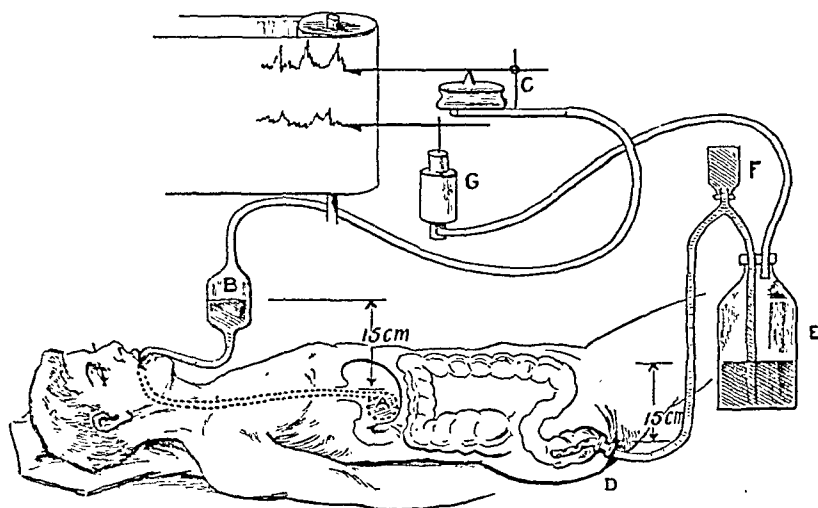


FIG. 1.—Technique of recording gastric and colonic activity. A, water-filled intra-gastric balloon containing 100 cc.; B, levelling bulb for excess balloon fluid maintaining hydrostatic pressure of not more than 15 cm.; C, recording tambour; D, rectal tube; E, bottle containing 2 liters of warm isotonic sodium sulphate with fluid level not more than 15 cm. above rectum; F, trap to withdraw flatus from siphon system; G, volume recorder.

Colonic Tone and Movement were measured and recorded by the apparatus represented in Fig. 1. The patients were prepared by 12 hours of fasting, a mild laxative the evening before, and a plain water enema at least 3 hours before the test. The colon was filled with isotonic sodium sulphate solution introduced through a siphon-tube leading from a reservoir adjusted to maintain a pressure of about 15 cm. of water. A tambour connected with the reservoir recorded movement of fluid into or out of the colon consequent upon changes in its tone or motility. Sodium sulphate solution was chosen because of its slight absorbability.

Roentgen Ray Observations were made by means of the usual barium meal or enema. In 1 instance the barium was introduced directly into the duodenum through a tube. For these observations I am indebted to Doctors F. P. Pendergrass, K. Kornblum and M. L. Allen.

RESULTS. When given subcutaneously the drug always produced the effects described by Starr, Elsom and Reisinger,¹ namely, flushing, sweating, salivation, fall of blood pressure, transient increase in pulse rate. When it was given by mouth these effects were so slight as to be detectable only by careful observation.

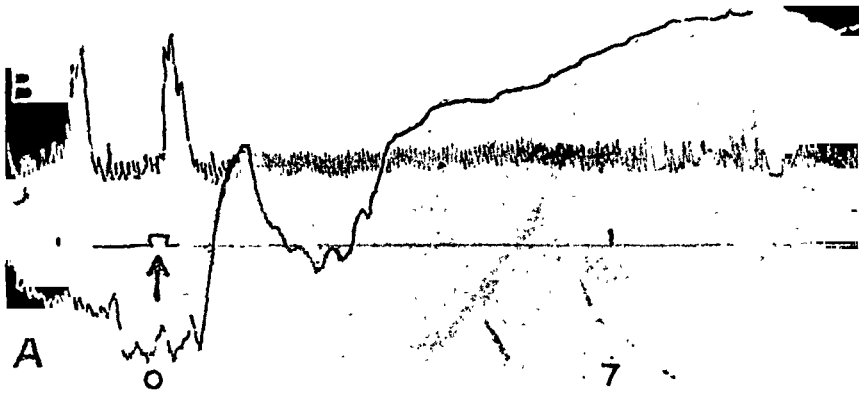


FIG. 2.—*A*, colonic tracing; *B*, gastric tracing (Fig. 1). Stomach empty for 12 hours previously. Given acetyl- β -methylcholin, 17 mg., subcutaneously. Colonic tone increased within 2 minutes, reaching a maximum in 8. Hunger contractions previously regular were abolished without alteration of tone.



FIG. 3.—*A*, colonic tracing; *B*, gastric tracing presumably from the antrum (Fig. 1). Patient ate a full meal 2 hours before the experiment. Given acetyl- β -methylcholin, 10 mg., subcutaneously with increase in both colonic and gastric tone and peristalsis. Maximum effect approximately 5 minutes after injection, coincident with the subsidence of the prompter cardiovascular reaction.

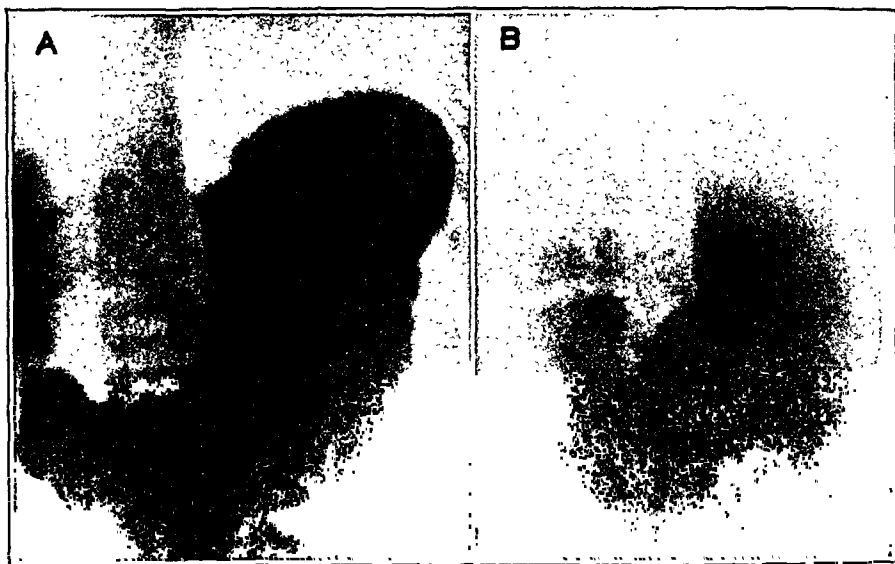


FIG. 4.—Roentgenograms of stomach. Ten milligrams of acetyl- β -methylcholin given subcutaneously. *A*, before injection stomach is somewhat relaxed with shallow peristalsis and fair motility of its contents, the duodenal "cap" being poorly filled; *B*, 5 minutes after injection gastric tone is increased, peristalsis deeper and more active forcing the gastric contents rapidly from the stomach and filling the duodenal cap.



FIG. 5.—Jejunal tracing recorded by water-filled balloon 30 cm. distal to ligament of Treitz. Acetyl- β -methylcholin, 400 mg. in 80 cc. of water, given by mouth. Marked increase in tone and peristalsis beginning within a minute. A minute perforation of the balloon allowed the pointer to fall steadily, thus recording less than the actual tonus response of the intestine.

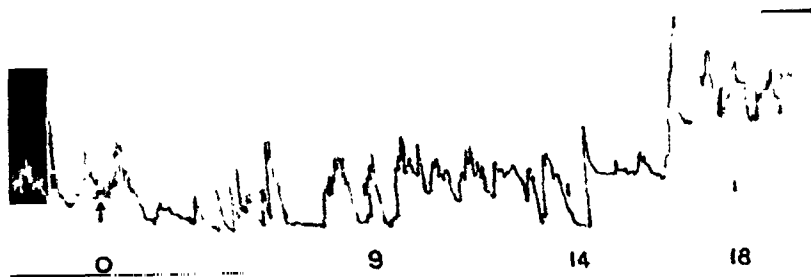


FIG. 6.—Jejunal tracing recorded as in Fig. 5, the balloon lying 35 cm. distal to ligament of Treitz. Acetyl- β -methylcholin, 15 mg., given subcutaneously. Prompt fall in tone and reduction in peristalsis during period of lowered blood pressure with subsequent marked rise in tone and increased peristaltic activity.

Action on Gastric Secretion. Action of acetyl- β -methylcholin on volume of gastric secretion was studied in 9 persons who showed no symptoms of gastro-intestinal disorder. The drug was tried both subcutaneously (5 to 10 mg.) and orally (200 to 300 mg.). In 2 cases, rather marked increase occurred; in 4, some increase was suggested; in none was there distinct decrease in volume. Precautions were taken against swallowing of saliva; in 8 out of the 9 trials, evidence of pyloric regurgitation was obtained by the detection of bile in the gastric contents withdrawn after the drug was administered. No marked change in acidity in these cases followed the administration of the drug. In 5 it was slightly decreased, in 1 increased, in 3, unchanged.

The drug was tested in 6 cases of hypochlorhydria. In 3 it caused a definite increase in acidity. In 2 of these, histamin gave a greater response in doses causing less systemic reaction than did acetyl- β -methylcholin. These results are recorded in Table 1. Those of previous gastric analyses obtained from the records of the hospital laboratory are recorded for comparison. Of the 3 cases in which no increase occurred, one received the drug by mouth and in another the subcutaneous dose was small (5 mg.).

TABLE 1.—EFFECT OF ACETYL- β -METHYLCHOLIN UPON GASTRIC SECRETION IN HYPOCHLORHYDRIA.

Case.	Sex.	Age.	Diagnosis.	Duration						
<i>Clinical Status:</i>										
1	F	37	Renal tuberculosis	6 mos.						
			Chronic duodenal ileus	5 yrs.						
2	F	20	Chronic duodenal ileus	18 mos.						
3	F	29	Chronic bronchitis	5 wks.						
Results in free HCl.										
Case.	Date.	Stimulant in addition to gruel.	1.	2.	3.	4.	5.	6.	7.	8.
<i>Secretory Studies:</i>										
1	5/30	0	0	0	0	0	11	49		
	7/32	0	0	0	0	0	0	0	0	0
	7/32	H. 0.3 mg.	0	0	0	0H	14	26	32	3
	8/32	A. 15.0 mg.	0	0	0	0A	10	10	18	14
2	9/31	0	0	0	0	0	0	0	0	0
	8/32	H. 0.3 mg.	10	0	0	0	0H	0	0	16
	8/32	A. 10.0 mg.	0	0	0	0	0A	9	12	13
3	8/32	A. 10.0 mg.	0	0	0	0A	5	19	8	32

NOTE.—Each case received 300 cc. of oatmeal gruel immediately after the first aspiration. Letters H and A stand for histamin acid phosphate and acetyl- β -methylcholin respectively. When placed after a figure in the table they signify that a subcutaneous injection of the indicated drug was given immediately after that aspiration.

In 3 cases of achlorhydria not due to Addisonian anemia or gastric carcinoma, neither histamin nor acetyl- β -methylcholin produced detectable secretion of acid.

From these results we may conclude that while acetyl- β -methylcholin in the doses tested has little action on normal gastric secretion, it may occasionally increase the secretion of acid in patients suffering from hypochlorhydria.

Gastric Motility. When the stomach was empty, subcutaneous administration of 7 to 17 mg. of acetyl- β -methylcholin or oral administration of 200 to 400 mg. was followed by cessation of the normal hunger contractions (Fig. 2). This was observed in each of 10 cases. Hypodermics of sterile water or administration of water or aromatic spirits of ammonia by mouth had similar but less prolonged effect.

The effect was different if the drug was given when the stomach contained food. In 5 cases increased peristalsis and tone followed the subcutaneous injection of 10 mg. (Fig. 3). In 2 of these cases and in 3 others the same effect on peristalsis was demonstrated by fluoroscopic observation after a barium meal (Fig. 4). In 1 of these the narrowing of the gastric outline identified increased tone. In another case the fluoroscope did not exhibit increased peristalsis but the balloon gave a record of increased tone.

It is therefore evident that the action of acetyl- β -methylcholin on motility varies with the physiologic condition of the stomach; when empty, contractions are diminished; when food is present either or both tonus and peristalsis are increased.

Action on the Small Intestine. Kymographic records were made of the response of the small intestine in 3 fasting subjects. In 1 the drug (400 mg.) was given by mouth. Both tone and peristalsis were immediately increased (Fig. 5). In the other 2 cases, the drug was given by subcutaneous injection (15 mg.). Tone and peristalsis were increased in both. This followed a transient decrease in peristalsis in 1; in the other, a decrease in tone (Fig. 5).

Roentgen ray study of the action of acetyl- β -methylcholin on the small intestine has been made in 5 individuals. In 4 of these the drug was given after a barium meal, in 1 after direct introduction of barium into the duodenum. In every case peristalsis was increased; in 1, the narrowing of the column of intestinal contents suggested increase in tone. The increase in motility resulted in hastened advance of the intestinal contents.

The predominant effect of acetyl- β -methylcholin on the small intestine is increase of peristalsis and tone.

Action on the Colon. Identification of action on the colon was more difficult than on the upper gastro-intestinal tract because of the irregularity of the graphic records during the control period. In each of 6 cases, however, the subcutaneous injection of from 5 to 15 mg. of acetyl- β -methylcholin caused elevation of tone which occurred within 2 minutes and lasted from 5 to 30 minutes (Figs. 2 and 3). In 3 of these peristalsis was increased; in 1 decreased; in 2 unchanged.

In 1 case 10 mg. were given subcutaneously while the colon, filled with a barium enema, was observed through the fluoroscope. Immediate increase in propulsive movement occurred.

After oral administration, the response, if any occurred, was

delayed. In 2 cases an abrupt increase in tone occurred 30 to 40 minutes after doses of 200 and 300 mg. This is the interval which Starr, Elsom and Reisinger found to elapse between taking the drug by mouth and signs of systemic action. In 3 cases, no action on the colon could be detected during the hour following oral administration of 200 or 300 mg. In 1 subject, 300 mg. of acetyl- β -methylcholin were given every 4th hour for 2 days. A barium enema was given before administration of the drug began and again 5 hours after the last dose. Comparative fluoroscopic observations indicated that the capacity of the colon had increased.

The above results indicate that increase in tone of the colon consistently follows subcutaneous administration of acetyl- β -methylcholin and that this is sometimes associated with increased peristalsis. In only a fraction of the trials did this result follow oral administration.

Routine Gastro-intestinal Roentgen Ray Examination. Slight to moderate increase of gastric peristalsis was observed in all of 6 cases receiving the routine barium meal following a course of acetyl- β -methylcholin by mouth. Each case had been studied immediately before the administration of the drug which was carried out in doses of 0.25, 0.6, 0.8, 0.9, 1.2, and 3 gm. respectively per 24 hours throughout the 2 days before and 3 days occupied by the examination. The degree of effect was proportional to the dose, the barium causing some nausea and pylorospasm in the case receiving 3 gm. per day. Small intestinal activity appeared unchanged but in spite of a distinct laxative effect in the 4 cases receiving the highest dosage the general impression of the fluoroscopist was of decreased colonic activity. In cases receiving 1.5 and 3.0 gm. per day colonic stasis seemed unequivocal.

CLINICAL STUDY. The experimental observations suggest that acetyl- β -methylcholin is fundamentally a stimulant to gastrointestinal motor activity and that with proper choice of dosage and method of administration one might count upon this taking place with fair regularity. Two conditions, constipation and post-operative distention have been used to test this effect.

Laxative Action. Few cases receiving 400 mg. or more of the drug by mouth have failed to note an increase in the number of their stools, though frequently smaller doses have been laxative. Movement of the bowels after subcutaneous injection occurs only occasionally. During a course of the drug frequent stools are passed during the first day or two, thereafter a decrease to 1 or 2 a day commonly occurring. Cramps have followed only so large a dose as 1 gm. by mouth.

Use in Postoperative Distention. In 9 of 14 cases of abdominal distention symptomatic relief followed the exhibition of the drug. This was accompanied by increase of peristaltic sounds over the abdomen, frequent expulsions of gas by rectum, and appreciable

reduction in the abdominal distention. Of the 5 cases unrelieved, 2 were observed to have increased peristaltic activity, 1 was unchanged and in 2 others observations were not made. In 1 of these, a patient of 68 years, bronchial spasm resulted with sufficient discomfort to warrant an injection of atropin which as usual abolished the effect of the acetyl- β -methylcholin promptly.

The 3 cases in which the most favorable results occurred are here reported in detail.

Case Reports. CASE 1.—E. C., a white male, aged 56 years, admitted for posterolateral sclerosis of Addisonian anemia, had recovered a normal blood count under liver therapy. His chief complaint, abdominal distention, had remained unabated for 2 weeks in spite of hot fomentations, turpentine stupes to the abdomen, an inlying rectal tube, repeated simple enemas, charcoal by mouth, and a nightly dose of 30 cc. of liquid petrolatum and 10 cc. of aromatic fluid extract of cascara. He was then given 200 mg. of acetyl- β -methylcholin by mouth, 3 times a day for 2 days without effect. When the dose was increased to 300 mg. the passage of flatus immediately began with complete relief of distention after the first dose. The drug was continued 3 times a day with no recurrence of symptoms for 3 days and then discontinued. Within 18 hours the distention and discomfort returned again to be controlled by the 300 mg. dosage. During the subsequent 5 months the patient has continued to get relief from doses of 300 mg. whenever distention has occurred.

CASE 2.—X. X., a white woman, aged 45 years, became markedly distended 24 hours after a laparotomy. While in considerable pain with frequent vomiting, 20 mg. of acetyl- β -methylcholin were injected subcutaneously. Immediately the abdominal pain increased, and for 10 minutes salivation and nausea were marked. Then copious expulsions of gas by bowel occurred continuing intermittently for $\frac{1}{2}$ hour. At the end of this time the distention had disappeared and the patient was relieved of her symptoms.

CASE 3.—H. B., a white woman, aged 36 years, developed phlebitis 18 days after a nephrotomy which had already been complicated by a brief postoperative atelectasis. Intractable abdominal distention followed, for the relief of which turpentine stupes and asafetida enemas had been totally ineffectual. A dose of 300 mg. of acetyl- β -methylcholin was given by mouth. Nausea resulted with belching and in $\frac{1}{2}$ hour the abdominal pain had markedly increased. No passage of gas occurred until a rectal tube was inserted 1 hour and 20 minutes after the administration whereupon immediate and copious expulsions occurred with relief of distention and abatement of symptoms.

Discussion. Motor stimulation as evidenced by increase in tone and peristalsis is the chief gastro-intestinal effect of acetyl- β -methylcholin, though secretory activity of the stomach may be at times increased. This conclusion is based upon the results of animal experimentation,⁴ special studies in normal individuals,¹ and the use of the drug in the clinical conditions described. Exceptions occur in the abolition of gastric-hunger contractions where the effect is apparently carminative in type, and in the decrease in activity of the small intestine during the period of vasodilatation

which follows a subcutaneous injection. This effect of vascular hypotension upon intestinal activity has been recognized in many conditions.⁵

Apparent discrepancies appear between the results of balloon experiments on the small gut and the fluoroscopic studies after a barium meal. In the latter method the absence of objective records necessitating a comparison of activity with one's recollection of that seen 5 days previously makes the identification of small changes very difficult. In most instances 2 hours or more elapsed between the study and the next preceding dose of the drug so that if any effect occurred it may have been already passing off. At least it suggests that repeated doses will not produce a state of continuous hyperactivity of recognizable degree. In the colon apparent contradiction is again present. Subjects, in whom the fluoroscopic study revealed some stasis, reported a laxative effect. This frequent defecation, as noted above, occurred chiefly in the first 2 days of a course while 3 to 5 days usually elapsed before the colonic study was made. Constipation was absent in all the patients taking acetyl- β -methylcholin even though but 1 stool a day was passed. This result, as in the case of the small intestine, suggests that a continuous effect could not be achieved by repetition of the doses at such intervals as were used in this study.

The secretory effects of the drug on the stomach even when it has been given subcutaneously have been less clearly demonstrable than the motor. Only in hypochlorhydria has hydrochloric acid secretion been unquestionably stimulated. Even here acetyl- β -methylcholin caused more discomfort to the patient for the increase in acidity elicited than did histamin. Because of the numerous factors influencing any study of gastric secretion by clinical methods, however, these results must be looked upon as merely suggestive.

When the drug is given by mouth in sufficient dosage, gastro-intestinal motor effects follow while the side effects are minimal. This is the method of administration to be preferred when this action is desired clinically. By means of it certain cases of distention have been relieved in which laxatives, enemas and stupes have been unavailing. It therefore seems probable that this drug will find a place in the treatment of certain gastro-intestinal disorders.

In conclusion I wish to acknowledge my indebtedness to Mr. J. P. English for his technical assistance, to the Radiologic Staff of the University Hospital for their coöperation in the Roentgen ray studies and to Drs. T. McK. Downs, F. A. Bothe, R. J. Veal and C. G. Jordan for their reports upon the effects of this drug in abdominal distention.

Summary. 1. Acetyl- β -methylcholin, by whatever route given, affects the gastro-intestinal tract as well as the other viscera supplied by the parasympathetic system. This effect is most satis-

factorily achieved by oral administration, secretory and cardiovascular activity dominating the picture after subcutaneous injection.

2. The usual gastro-intestinal effects are an increase in tone and movement. This is not the case in the fasting stomach or in the small intestine during the period of falling pressure after subcutaneous injection.

3. Beneficial clinical effects have been manifested by slight stimulation of gastric secretion in some cases of hypochlorhydria, by a comfortable laxative effect in most individuals taking large doses by mouth, but chiefly in the relief of abdominal distention in certain instances in which the usual procedures had failed.

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ACETYL- β -METHYLCHOLIN.

III. ITS ACTION ON PAROXYSMAL TACHYCARDIA AND PERIPHERAL VASCULAR DISEASE, WITH A DISCUSSION OF ITS ACTION IN OTHER CONDITIONS.

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IN the investigation reported in a preceding communication¹ it was demonstrated that the subcutaneous injection of acetyl- β -methylcholin into normal persons was promptly followed by a vigorous but not dangerous type of action, the more usual manifestations of which were marked flushing, sweating, and salivation, accompanied by a fall in blood pressure and a rise of pulse rate. The acute stage of this action lasted only 2 or 3 minutes; all the symptoms passed off within 15 or 20 minutes. When given by mouth the action was mild. No uncomfortable or alarming manifestations were ever produced. A gradual fall in blood pressure and pulse rate usually took place but the other symptoms occurred with less frequency.

Pharmacologic studies have shown^{2,3} that part of the action of this drug is similar to that which follows stimulation of the vagus

nerve and other parts of the parasympathetic nervous system. Therefore, it seemed proper to try to utilize this effect to benefit cases of paroxysmal tachycardia, a condition in which the attack may often be arrested by vagus stimulation. Another effect of this drug is peripheral vasodilatation, and we have sought to employ this type of action in the treatment of the spastic types of peripheral vascular disease. The purpose of this communication is to report the results of our study of the drug's action in these and certain other types of cardiovascular disease and to point out additional aspects of its action which might be useful in the treatment of other conditions. If given subcutaneously in adequate dosage the drug brings most attacks of paroxysmal tachycardia to an end immediately. Given by mouth it causes the relaxation of the arterial spasm of Raynaud's disease, provided the spasm is not too severe, and has been used with success in the symptomatic relief of certain patients suffering from this and other conditions in which vascular spasm occurs. The results obtained in other cardiovascular conditions are less striking but certain cases of headache were undoubtedly relieved.

The Utility of the Vagus Action. *The Effect on Paroxysmal Tachycardia.* Twenty-nine attacks of this condition in 9 patients have been treated by injections of acetyl- β -methylcholin. Electrocardiograms obtained in all but 2 patients showed the attacks to be of the auricular or supraventricular type. I am indebted to Drs. B. I. Comroe, F. W. Burge, and J. M. Hayman for a report of the results in cases M. F., W. S. (Attacks 1 and 2) and P. R. respectively. I am also indebted to Dr. F. C. Wood for making and interpreting the electrocardiograms.

In the large majority of instances an attempt was made to stop the attack by pressure on the carotid arteries high in the neck before the drug was given. This procedure, commonly known as vagus pressure, has been demonstrated by Hering⁴ to produce its effect by means of a carotid sinus reflex and not by direct vagus stimulation. Therefore, it will be spoken of as carotid pressure in this paper. Twenty attacks were brought to an end by this means alone during the course of the investigation.

If carotid pressure was unsuccessful the drug was given subcutaneously. In typical cases flushing of the face and neck appeared in about a minute. A few seconds later a brief cardiac pause occurred, followed by a momentary period of irregularity of both rhythm and intensity of heart sounds and pulse, and then by normal rhythm. The blood pressure diminished from 10 to 20 mm. during the height of the action and the pulse became weaker. Increased depth of breathing, sweating and salivation also occurred. The drug's action passed off in a few minutes leaving the heart beating normally.

In the latter half of the investigation a technique was developed

to terminate attacks when the simple injection of the drug was insufficient. If any attack did not stop promptly after the appearance of the flush, the site of the injection was massaged vigorously, with a resulting increase in the intensity of the drug's action. If the attack still persisted the carotid sinuses were compressed alternately, while the drug's action, as judged by the flush, was still undiminished. This was usually immediately successful, although similar carotid compression before the administration of the drug had been ineffective.

Four electrocardiographic records of transitions from paroxysmal tachycardia to normal rhythm after the administration of acetyl- β -methylcholin have been secured. Typical records are shown in Figs. 1 and 2. One shows transient slowing, then a pause followed by immediate resumption of normal rhythm. In the other, cessation of the paroxysm is followed by a period of marked slowing, with prolongation of the *P-R* interval up to a maximum of 0.32 second, occasional extrasystoles, a few blocked auricular beats and aberrant ventricular complexes suggesting an impairment in bundle-branch conduction. This momentary period of disturbance was followed by normal rhythm, at first at a slow rate. The rate increased as the action of the drug passed off and then slowly diminished. These effects are similar to those which can be produced by vagus stimulation and they should be attributed to this action of the drug. Comparable effects have been observed in the isolated heart in animal experiments.³

In a very sick man, C. M. K., a different effect was observed (Fig. 3), the small doses of acetyl- β -methylcholin producing momentary complete block which reverted again to tachycardia. This patient had received 1 gm. of digitalis during the preceding 24 hours and he had been taking smaller amounts previously. As part of the action of digitalis is similar to that of vagus stimulation, and as block so frequently follows an overdose of this drug, it seems reasonable to suppose that the vagus effects of digitalis and acetyl- β -methylcholin might reinforce each other and thus produce block in this instance. But in two experiments on cats,³ the effect of intravenous injections of acetyl- β -methylcholin on the pulse rate was not changed by the administration of large doses of digitalis.

The results are recorded in Table 1. Those obtained on T. H. in Attacks 9 to 19 were so similar to those secured in the preceding attacks that they have been omitted from this table. A subcutaneous injection of 30 mg. or more of acetyl- β -methylcholin combined with carotid pressure in the few instances noted in the table promptly brought to an end 24 attacks of paroxysmal tachycardia in 7 adult patients. In the case of an emaciated boy (W. S.) smaller doses were successful on 3 occasions. In 2 instances, in T. H., the cessation of the paroxysm was momentary, in the others the period of normal rhythm coincided with that usually occurring

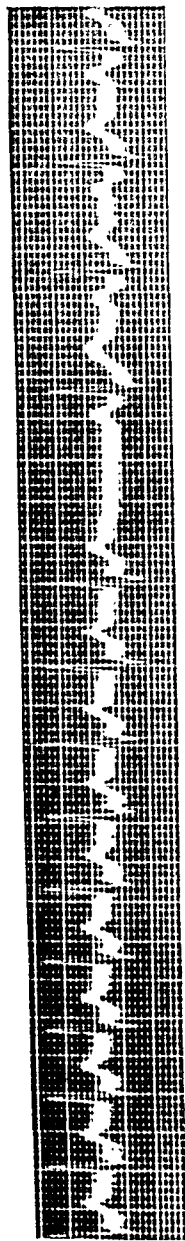


FIG. 1.—Transition from paroxysmal tachycardia to normal rhythm following the administration of acetyl- β -methylcholin.

Lead 2. Thirty milligrams injected 45 seconds before the beginning of the record shown. The lower section is continuous with the upper. (Case A. M. K.)

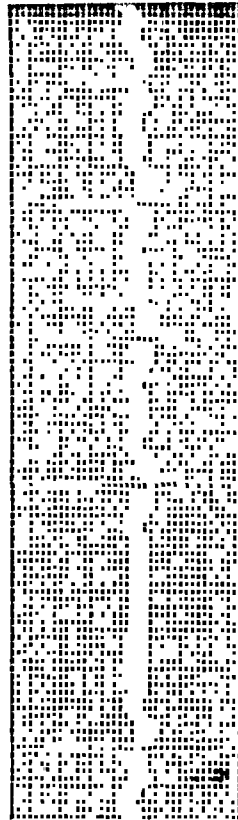
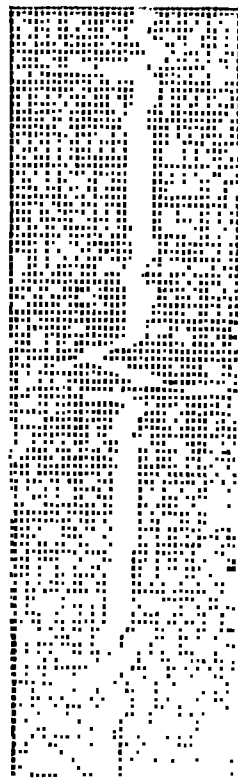
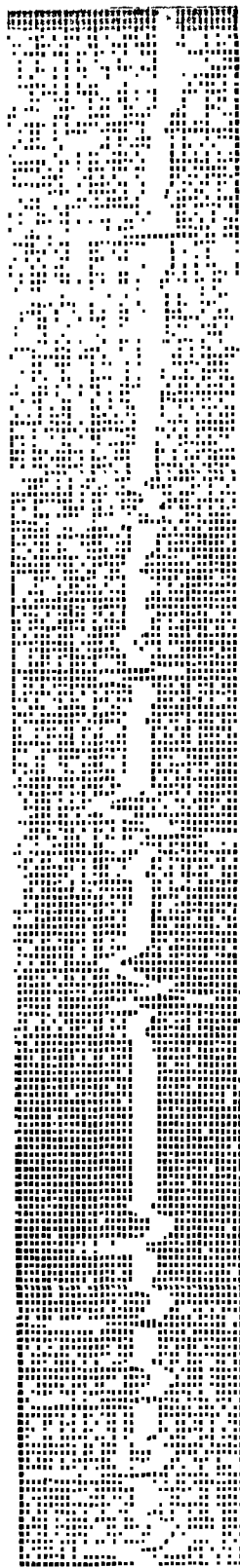


FIG. 2.—Transition from paroxysmal tachycardia to normal rhythm following the administration of acetyl- β -methylcholin.

Lead 2. Thirty milligrams injected about 2 minutes before the beginning of the record. The lower section is continuous with the upper. (Case T. H.)

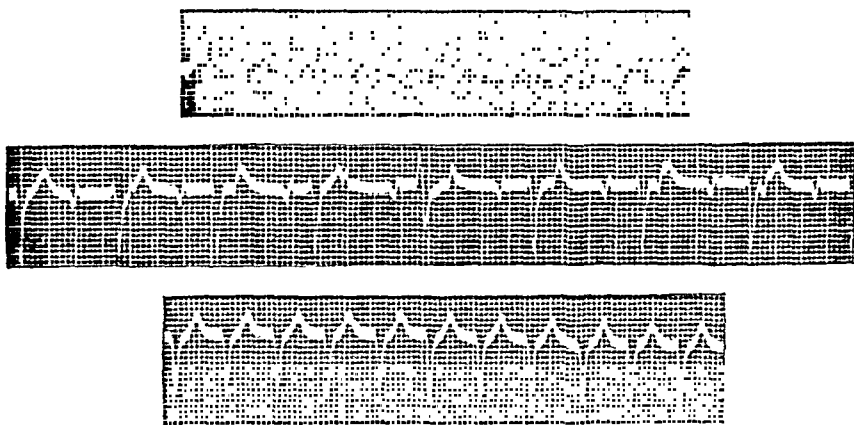


FIG. 3.—Transient heart block following an injection of acetyl- β -methylcholin in a patient with paroxysmal tachycardia who had received large doses of digitalis.

Lead 2. The upper record was made before the drug was administered. The middle record was taken about 2 minutes after the injection of 15 mg. The lower record was made about 2 minutes later. (Case C. M. K.)

TABLE 1.—EFFECT OF ACETYL- β -METHYLCHOLIN ON ATTACKS OF PAROXYSMAL TACHYCARDIA.

Patient.	Age.	Additional diagnoses.	Number of observed attacks.	Type of tachycardia by eeg.	Unsuccessful therapy before ABMC.	Dose of ABMC, mg.	Pulse rate before.	Pulse rate after.	Approx. time betw. injec. and cessation of attack (min.).	Remarks.
F. C.	26	Rheumatic heart disease, Class II A	1	Auricular	Carotid and ocular pressure; vomiting; 1.2 gm. quinine	35	180	80	1	
A. M. K.	49	Neurocirculatory asthenia	1	Auricular	Carotid pressure	30	170	120	4	Patient usually had pulse rate over 100 when not in attack.
M. F.	42	Three days after thyroidectomy	1	Unknown	10 mg. morphin	20	250	200	..	Paroxysm continued or resumed.
P. R.	50	Polycythemia	1	Supraventricular	Carotid pressure	30	250	153	3	Paroxysm stopped. Rate similar to that before attack.
B. M. K.	21	Rheumatic heart disease, Class I	1	Supraventricular	Carotid pressure	30	160	114	7	Carotid pressure during drug's action unsuccessful; attack stopped several minutes later.
C. M. K.	45	Pelvic abscess; shock; blood pressure not obtainable; fever for 6 months	1	Supraventricular	Carotid pressure; 1 gm. digitalis; 0.5 gm. quinin	5	146	Momentary heart block, paroxysm resumed.
						5	150	One-half hour later—no effect.
						10	146	One-half hour later; transient block resumption of paroxysm with changed eeg
						15	150	Patient vomited and coughed after attack stopped.
W. S.	19	Ulcerative colitis; anemia	1	Carotid pressure	20	1	Stopped.
			2	Supraventricular	Carotid pressure	10	225	85	4	Vomited, defecated after cessation.
			3	Supraventricular	Carotid pressure	15	225	Vomited, defecated after cessation.
			4	Supraventricular	Carotid pressure	12	204	Failure.
			1	Auricular	Carotid pressure	12	200	Second failure 3 hours after first.
T. H.	59	Arteriosclerosis; cardiac hypertrophy	1	Auricular	Carotid pressure	10	155	Failure.
			2	Auricular	Carotid pressure	20	150	83	..	Failure.
			3	Auricular	Carotid pressure	30	168	60	4	Attack stopped but resumed promptly.
			4	Auricular	Carotid pressure	40	170	70	2	No resumption.
			5	Auricular	Carotid pressure	50	180	55	3	Carotid pressure during drug's action.
			6	Auricular	Carotid pressure	50	160	88	4	Carotid pressure during drug's action.
			7	Auricular	Carotid pressure	50	165	70	1	
			8	Auricular	Carotid pressure	50	160	75	2	
			1	Unknown	Carotid pressure	50	185	70	5	Attack stopped, resumed, stopped and resumed again; after carotid pressure, while drug was still acting, it stopped permanently.
W. T.	60	Diabetes; arteriosclerosis; gangrene of foot; amputation 15 days ago	1	Unknown	Carotid pressure	30	200	100	..	Unsuccessful, very little action of any kind.
						50	220	Given about 12 minutes after preceding dose.

between attacks. The few failures occurred with doses under 30 mg. or at the hands of persons who neither massaged the site of the injection nor compressed the carotids during the drug's action. In the case of C. M. K. we started with minute doses because the patient was so very ill, and failed to go higher because we wrongly interpreted the slower rate and increased excursion of the galvanometer string to mean that the attack was over.

In the patients with tachycardia the side effects of the drug usually appeared more slowly and were much less intense than those which followed the administration of similar doses to normal persons. In the arteriosclerotic men T. H. and W. T., doses of 30 mg. or less given during the paroxysm were followed by little demonstrable effect of any kind; 50 mg. produced the usual effects and stopped their attacks. On the other hand doses of 20 mg. or less produced marked side effects on the boy W. S. This difference is doubtless due to slower absorption of the drug from the subcutaneous tissues when the circulation is embarrassed; this must be remembered in choosing the initial dose for any patient. It seems proper to start with small doses. A larger dose may be given as soon as the effects of the preceding have passed off; *i. e.*, in about 15 minutes.

The patients usually had a certain amount of discomfort during the height of the drug's action. It passed off in a few minutes. They all agreed that it was far overbalanced by the relief from distress which followed the cessation of the paroxysm.

The attempt was made to prevent the onset of attacks by giving acetyl- β -methylcholin by mouth. T. H. was having attacks several times a week. He was given the drug 4 times a day and the dosage was increased until he took 4 grams daily. The larger doses appeared to diminish the number of attacks somewhat but they produced an annoying diarrhea. Quinidin was far more effective in preventing attacks and is doubtless a superior drug for this purpose.

Action on Other Types of Tachycardia. We have made a few observations on the effect of acetyl- β -methylcholin in tachycardia other than the paroxysmal type. A patient with thyroid disease and a pulse rate of about 150 was given increasing doses of acetyl- β -methylcholin by mouth to a maximum of 600 mg. No slowing of the pulse followed. A subcutaneous injection of 20 mg. increased the pulse rate.

Two patients with constant tachycardia of unknown origin, both young girls, were given by mouth 300 and 40 mg. respectively. After the larger dose the heart rate fell from 110 to 80 and remained at the lower level for 40 minutes. The smaller dose had no effect. The effect of prolonged administration of the drug to such patients has not been ascertained.

Action in Auricular Fibrillation. It has been demonstrated that the slowing of the ventricular rate which occurs in this condi-

tion after the administration of digitalis is to be attributed in large part to an action similar to that which follows vagus stimulation. Therefore it seemed possible that acetyl- β -methylcholin, which has a similar action, might likewise cause a desirable slowing of the rate in these cases.

Two cases were selected whose rapid ventricular rate persisted after digitalis had been pushed until nausea and vomiting occurred. The first was given doses of 20 and 40 mg. subcutaneously while connected to the electrocardiograph. The smaller dose did not affect the rate; after the larger the ventricular rate fell from 170 to 112, then returned to 143 after the effects of the drug had passed off. This apparently beneficial effect was accompanied by a good deal of discomfort to the patient from the side effects of the drug. In the second case a subcutaneous dose of 5 mg. caused a fall in rate from 108 to 86. The slowing was momentary and the rate then returned to its original level. Though there was no discomfort in this case the slowing was certainly too transient to be of therapeutic value.

Three cases were selected in which digitalis had failed to produce satisfactory slowing of the ventricular rate. While the digitalis was continued, doses of acetyl- β -methylcholin up to 1 gm. were given by mouth. No slowing could be demonstrated. Therefore we believe that these patients with auricular fibrillation, resistant to digitalis, were not benefited by acetyl- β -methylcholin.

The Utility of the Vasodilator Action. *The Effect in Raynaud's Disease.* Four cases of this disease have been studied. They complained that their hands became "bloodless" or blue and painful on exposure to cold in the winter. In each case the hands developed marked cyanosis on immersion in water at 15° C. for 20 minutes. The mildest case, Mrs. G. S., aged 26, suffered only when she drove her automobile in winter. The most severe, Mrs. E. I., aged 60, had gangrenous spots on 2 of her fingers, and the depressed scar of a healed lesion on a third. Essential hypertension complicated this case. Miss F. S. and Mr. M. C., aged 26 and 24, were moderately severe cases but neither had had gangrenous spots. They were otherwise in good health.

Several experiments were made to test the effect of the drug. Skin temperatures were determined by thermal junctions usually fastened to the skin with wide strips of adhesive to prevent evaporation of sweat from cooling the adjacent skin. The skin color was judged by means of the color scale devised for this purpose by Lewis.⁵

F. S., having come in from outside, was placed in a cool room, the temperature being 13° C. At the beginning of the observation the hands ached and were cold and pale. The temperature of the fingers proximal to the nails ranged from 20.1° C. to 22° C. The patient was then given 30 mg. acetyl- β -methylcholin by mouth. One hour later the characteristic action of the drug set in, the blood pressure fell from 102/74 to 90/60, the pulse rate diminished from 92 to 76 and the appearance of the hands com-

pletely changed. They were now warm and redder than normal. The warmest finger was now 32° C., the coldest 24.6°. The discomfort in the hands had lessened but a certain amount still persisted. An hour and a half later the blood pressure had returned to 108/65 and the pulse rate had risen to 88. The hands had become pale again, the skin temperatures had diminished, and now ranged between 22° and 23°. This striking demonstration of the relief of the spasm of Raynaud's disease by means of acetyl- β -methylcholin was repeated on 2 other days, with oral doses of 40 mg. and 100 mg. of the drug.

In 2 other cases, G. S., and E. I., evidence of the vasodilating action of the drug was sought by a comparison of the effects of immersing the hands in cold water at 15° C. for 20 minutes before and during the drug's action. The cyanosis which appeared on the second immersion was not strikingly different from that produced before the drug was given. The changes seen were in the direction of greater redness during the action of the drug. Much more striking was the difference in the patient's sensations. Both stated that on the first immersion the hands became numb and the cold caused no discomfort. But during the drug's action numbness did not occur and they suffered severely from the cold. This may be interpreted as indicating that during the drug's action enough circulation persisted to maintain the function of the nerves. However, the results clearly demonstrate that the drug will not prevent the typical spasm of Raynaud's disease if the hands are exposed to severe cold.

On another occasion spasm was produced in E. I. by immersion of the hands in cold water. After withdrawal the patient lay down and 5 mg. of acetyl- β -methylcholin were administered subcutaneously. Two minutes later the face flushed and a few minute red spots appeared in the cyanosis. Ten minutes later 10 mg. of acetyl- β -methylcholin were administered subcutaneously. This caused marked flushing of the face, and the arms reddened down to the area of cyanosis, but the color of the hands remained unchanged although the skin temperature of the fingers which had been slowly rising, started to climb more rapidly. The action of the drug passed off before any further change could be demonstrated. Obviously the drug had but little effect on such high grades of spasm. This is not surprising as in such conditions the blood flow has practically ceased and the drug would not reach the vessels affected.

In an attempt to relieve the symptoms, acetyl- β -methylcholin was prescribed to the 3 most severe cases.

F. S. was given 20 mg. 3 times a day by mouth. A week later the patient stated that she could detect some slight effect. The dosage was then slowly increased until it reached 100 mg. This dosage was taken 3 times a day and the patient thought her symptoms were improved but relief was not complete. Later the patient took the drug only when she expected to be exposed to cold. This seemed to be a better method, relieving the symptoms while she was in the cold but she continued to have some discomfort when, on reëntering the house, her hands became "hot and swollen."

M. C. was instructed to take 30 mg. 3 times a day. A week later he reported that his symptoms had been almost completely relieved, although the weather had been much colder than in the preceding 2 weeks. He stated that his hands tingled a little when he had exposed them doing outdoor work, but they did not get white, blue and numb as they had done before. The patient was provided with more of the medicine, but he obtained work in another city and the case could not be followed further.

E. I. was first seen in February, 1932. She complained that spasm was present almost every morning while she was doing her housework. She

was, therefore, given two bottles of medicine, each containing acetyl- β -methylcholin and told to take a dose of 100 mg. from the first bottle whenever a spasm occurred. If her hands had not warmed up in an hour, she was to take a similar dose from the second bottle. A week later the patient reported that each time she took the first dose her hands warmed up in 40 or 50 minutes and that they then stayed warm all day. She had taken the second dose only once and was greatly pleased with the relief which she had obtained. Without the patient's knowledge, the contents of the bottle to be taken first were changed to an inert solution with a bitter taste. The bottle containing the medicine to be taken second contained acetyl- β -methylcholin as before. A week later the patient reported that the first medicine was now ineffective and that she had had to take the second medicine every day, and that it had relieved her symptoms in about an hour. This seemed to be sufficient demonstration that the patient was really getting relief from the drug. She was, therefore, told to take 100 mg. every morning which was cold enough to cause symptoms. She was seen a month later and had been taking the medicine regularly. The gangrenous spots on the fingers had healed and she was practically free of symptoms. However, warmer weather had now begun and was certainly a factor in the improvement.

During the following spring and summer she took the drug only on exceptionally cool days, and during the fall she resumed it with increasing frequency until with the coming of winter she again took it daily. In December and January, she took 50 mg. after breakfast "to prevent spasm," whenever the weather was cold. This was not always sufficient. If spasm did set in she took 100 mg. and relaxation always occurred in about an hour. Under this program she insists that she was very much more comfortable than she had been in any winter during recent years. Relief was not complete and during December one of her fingers became sore and an ulcer developed at its tip. This lesion healed in 2 weeks, whereas three similar lesions occurring in former years had not healed until spring.

These observations may be summarized as follows: In Raynaud's disease, the drug does not prevent the development of vascular spasm when the hands are exposed to severe cold. Nor does it cause prompt relaxation of the spasm so produced. However, it can overcome or prevent that which follows more moderate exposure. The patients agreed that their symptoms were in part relieved when the exposure was limited to that encountered in their usual occupations.

Action in the Occlusive Types of Peripheral Vascular Disease. In the conditions in which the main vessels of a limb are occluded by organic disease, phenomena suggesting spasm of the unobstructed vessels may often be demonstrated. Therefore, it seemed desirable to ascertain whether these patients might not be benefited by acetyl- β -methylcholin.

The first experiment was made on J. N., aged 28 years, a patient with thromboangiitis obliterans of 2 years' duration. No pulse could be felt in the arteries of either foot and gangrene had necessitated the amputation of the terminal phalanx of both great toes. Three weeks after the operation his feet were exposed to cold air at a temperature of 16° C. The skin temperature of the toes began to fall rapidly and pain soon commenced in both feet. He was then given 300 mg. acetyl- β -methylcholin by mouth. About an hour later the usual signs of the drug's action were observed,

the skin temperature of the toes stopped falling and began to rise and the discomfort disappeared. When the period of observation was terminated 1½ hours later, the temperature of certain toes was still rising, that of other toes was beginning to fall. The maximum increase observed was 1.8° C. As the room temperature did not change the small rise of skin temperature must be attributed to vasodilatation caused by the drug. Similar experiments conducted with doses of 75 and 200 mg. gave essentially similar results.

The same experiment was performed in 2 other cases. In a case of diabetes with threatened gangrene of the left foot a dose of 500 mg. by mouth was followed by a rise of temperature in the more normal foot while that of the threatened foot continued to fall. In another diabetic who had a poor circulation in both feet with severe lesions on one, doses of 100 and 300 mg. did not interrupt the steady fall of skin temperature, though there was other evidence that the drug was acting. These results suggest that the drug will benefit only certain patients, doubtless those in whom vascular spasm is present. But if the vessels are occluded solely by organic disease acetyl- β -methylcholin does not increase the blood supply to the extremity.

When the drug is injected subcutaneously the effect on the peripheral vessels is different. A diabetic whose foot eventually became gangrenous was given a subcutaneous dose of 30 mg. This was followed by a more rapid fall of skin temperature in the foot, evidence that the drug's action diminished the circulation. A similar result was obtained in another case of this disease. Subcutaneous injections appear to be contraindicated in the treatment of such conditions. The fall in blood pressure which follows this method of administration not only diminishes the head of pressure in the peripheral arteries but also may call forth a compensatory vasoconstriction which overcomes the dilator action of the drug.

Since the evidence indicated that the drug, given by mouth, caused an increase in the circulation to the feet of certain cases of occlusive peripheral vascular disease, it has been tried in the treatment of threatened gangrene of the feet. The patients chosen suffered from severe pain in the diseased foot, and an attempt was made to determine the effectiveness of the treatment by the relief secured when the patients did not know whether they were receiving the drug or not.

Mr. C. B., aged 53 years, was known to have had diabetes for 35 years. The toes were cyanotic and vessels of the feet did not pulsate. He had suffered severely from pain in the left foot for 2 weeks and blebs had formed on the toes. The threatened foot was placed in a thermoregulated foot cradle with partial relief but pain persisted at night. Four days later the patient was given 500 mg. of acetyl- β -methylcholin in milk at 6 and 8 P.M. After this the patient had no pain at all; his first comfortable night for almost 3 weeks. The drug was given again the next night and the relief persisted. The night following it was withdrawn and an inert bitter

substance added to the milk which was given as before. This night the patient complained of pain, though it was not as severe as before the drug had been given. The acetyl- β -methylcholin was then resumed for 3 days and discomfort disappeared. Then it was again interrupted and slight pain reappeared, to disappear when the drug was resumed. Therefore, there can be no doubt that the drug relieved the patient's pain. The lesions healed also and recovery was uneventful.

Mr. W. J., aged 58 years, had noted pain in the right foot 3 months ago. One month before admission a small gangrenous patch appeared on the toe and a chronic ulcer on the heel. He went to a hospital and was treated for a month without relief of pain at night. He was then sent to the University Hospital. At that time the left foot was markedly cyanotic and no pulse could be felt below the popliteal space. During his first night in the hospital the patient suffered severe pain. The next day he was given doses of 200 mg. acetyl- β -methylcholin every 2 hours from 4 until 10 P.M. Following this he passed the night without pain and stated that it was the first time this had happened for a month. The next day without the knowledge of the patient an inert mixture was substituted for the acetyl- β -methylcholin. He had no pain that night nor did it recur during his stay in the hospital. Therefore while the initial relief of pain may have been due to the acetyl- β -methylcholin we have certainly failed to prove it.

Mr. E. A., aged 60 years, was known to have had diabetes for 1 year. No pulse could be felt in any artery in his feet. The left foot showed marked rubor, and there was an ulcer between the 4th and 5th toes. Pain had been severe for the last 3 weeks, especially at night. The first night he was given 500 mg. acetyl- β -methylcholin by mouth, the next night 1 gm. No relief followed, and the eventual cessation of pain is certainly not to be attributed to the drug.

Mr. A. C., aged 45 years, had had thromboangiitis obliterans for 3 years. Gangrene had led to amputations below the left knee and above the right ankle. Six weeks ago, after slight trauma, a spot of gangrene developed on the terminal phalanx of the left little finger and the rest of the finger became swollen and cyanotic. Pain in that area soon became intense especially at night. Five doses of morphin sulphate each gr. $\frac{1}{4}$ (15 mg.) failed to relieve it on one occasion. Two weeks before admission a periarterial sympathectomy had been performed, without relief of pain or other improvement. After admission the pain at night was sufficient to prevent much sleep, he was usually comfortable during the day. He was therefore given 500 mg. of acetyl- β -methylcholin in milk at 6 and 9 P.M. The first night after this treatment pain was much diminished, the second night he had no pain at all. Then the drug was omitted, the milk containing an inert bitter substance being given as before. The night following he had a violent attack, morphin gr. $\frac{1}{4}$ (15 mg.), phenobarbital gr. ij (120 mg.), amyl nitrite m. iii (0.18 cc.) repeated once, nitroglycerin gr. 1/100 (0.6 mg.) and finally sodium amytal gr. iii (0.18 gm.) were given with but little relief; the pain gradually subsiding 1 hour after the last dose. The next night he had no pain. The night following violent pain returned. After morphin sulphate gr. $\frac{1}{4}$ (15 mg.) had been ineffective, he was given 500 mg. of acetyl- β -methylcholin by mouth. The pain remained the same for the next 2 hours. Twenty mg. of acetyl- β -methylcholin were then given subcutaneously. The pain in the finger was at once relieved but the side effects of the drug were unusually severe, probably because the action of the previous dose was still in effect. The patient became dyspneic and complained of substernal pain so that atropin sulphate gr. 1/200 (0.3 mg.) was given subcutaneously to stop its action. This did not result in a

return of the pain in the finger, and the patient slept well until morning. The next night there was another violent attack of pain, as severe as the previous night. A smaller dose, 10 mg. of acetyl- β -methylcholin was given subcutaneously. There was no uncomfortable reaction but the pain was not promptly relieved. It subsided gradually.

At this point the administration of 500 mg. of acetyl- β -methylcholin by mouth at 6 and 9 p.m. was resumed. The pain at once diminished and then disappeared completely. The skin temperature of the finger improved and the lesion began to heal. Unfortunately this promising treatment could not be continued as the available supply of the drug was exhausted. Therefore, thoracic sympathectomy was performed. There seems no doubt of the relationship of the drug to the relief of pain in this case.

The effect of acetyl- β -methylcholin on the pain of these 4 cases of occlusive peripheral vascular disease has been illustrated in Fig. 4. In 2 of them the relief may fairly be attributed to the

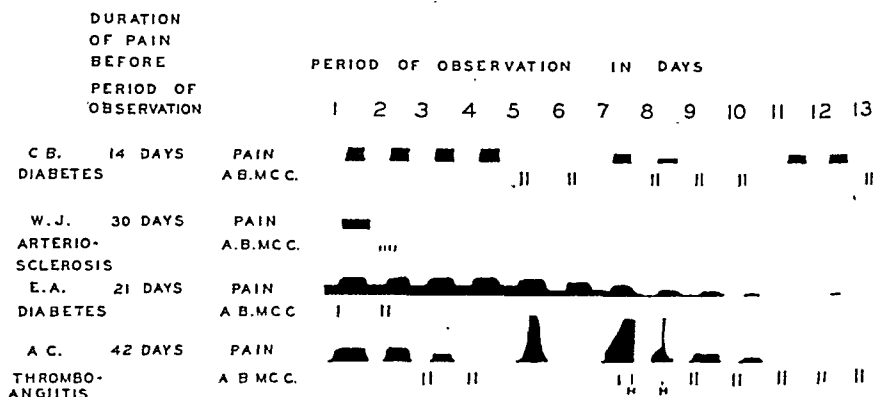


FIG. 4.—Effect of acetyl- β -methylcholin on the pain of 4 cases of obstructive peripheral vascular disease. The larger bars indicate doses of 500 mg., the smaller 200 mg. H, indicates a hypodermic injection, the other doses were given by mouth.

drug, in another this may be the case, in the fourth the drug was entirely ineffective. The patients benefited were doubtless those who had some spasm in addition to their organic obstruction.

Effect on Hypertension and Headache. Moderate doses of acetyl- β -methylcholin given subcutaneously to patients with hypertension were usually followed by a larger fall of blood pressure than that which occurred in normal persons. The maximum fall observed, from 260/160 to 145/95, occurred after a dose of 25 mg. As the action passed off the pressure returned to its previous height. The patients were all more uncomfortable during the action of the drug than before or after it, and we do not believe that they were benefited.

When the drug was given by mouth many patients exhibited a considerable fall of blood pressure which lasted for $\frac{1}{2}$ hour or longer

without annoying symptoms. Doses of from 50 to 400 mg. have been given on 8 occasions to patients with hypertension who were confined to bed for the day of the test. In 1 patient 200 and 400 mg. failed to cause any effect. In the others the fall of systolic pressure ranged from 38 to 16 mm.

In 3 patients with hypertension relief of headache was reported after taking the drug. One of these was given 100 mg. twice a day by mouth. Her headache returned when the drug was omitted without the patient's knowledge, and it was relieved when the drug was resumed. On the other hand in 3 apparently similar cases the drug did not relieve the headache.

Patient E. I., who has essential hypertension as well as Raynaud's disease, has taken from 50 to 100 mg. of acetyl- β -methylcholin very frequently for 16 months. At the end of this period her blood pressure (220/130) was identical with that found before she began treatment.

The Effect on Various Intracranial Conditions Possibly Associated With Spasm of Cerebral Vessels. In a comatose patient, M. B., with hypertension and Cheyne-Stokes breathing, an effect on respiration was demonstrated by Dr. C. F. Schmidt. A subcutaneous dose of 30 mg. was followed by a fall in systolic blood pressure from a maximum of 228 to a minimum of 110 mm., and the breathing became regular and remained so. Twenty-six minutes later 1.2 mg. of atropin sulphate was administered and Cheyne-Stokes breathing reappeared within 5 minutes, the blood pressure rising from 160 to 190 mm. The next day a very similar fall in blood pressure was caused by venesection but the Cheyne-Stokes breathing persisted. Therefore the cessation of Cheyne-Stokes breathing after the drug cannot be attributed to changes arising from the fall in blood pressure, and an action on cerebral vessels is suggested. With this evidence before us we attempted to treat patients having certain ill-defined conditions in which it was suspected that spasm of cerebral vessels might be a factor.

A patient, Mr. J. E., was subject to severe and frequent headaches in one-half of his head. The case was diagnosed cerebral vascular spasm by Dr. W. G. Spiller. The patient was given large doses of the drug, 4 gm. daily for 20 days, and later for 14 days. He was convinced that the pain was materially lessened by the drug. But there was a neurotic element in the case, and suggestion rather than drug action may have caused the improvement.

Another patient, Mrs. A. A., suffered from attacks of vertigo, fairly typical of Ménière's disease. She was not relieved by sedatives or quinin. When given 500 mg. of acetyl- β -methylcholin by mouth she insisted that she was greatly relieved and demonstrated it by walking to the bathroom which she had previously been unable to do without falling. The vertigo returned when the drug was omitted. Its resumption was again followed by improvement.

Miscellaneous Results. We tried the effect of a subcutaneous dose of 10 mg. in a case of hemiplegia whose rapid and complete recovery from two previous attacks suggested that it might have been caused by vascular spasm. No beneficial effects were observed.

Encouraged by the relief from headache demonstrated in a few cases of hypertension, we have tried the drug in other types of headache, especially migraine. No relief followed in 2 cases. One patient insisted she was relieved, but in a subsequent attack no relief followed.

Two cases of angina pectoris were given 20 mg. of acetyl- β -methylcholin subcutaneously during an attack. The symptoms of the drug's action appeared as usual but the pain continued unabated. Later nitrites relieved it.

Discussion of the Clinical Utility of Acetyl- β -methylcholin. No final evaluation of this active drug can be made on the basis of this, the initial clinical investigation. We have followed only a small number of the leads suggested by its pharmacologic activity. It is of interest to consider other possibilities and point out the limitations of the present investigation.

Acetyl- β -methylcholin may be thought of as a physiologic antagonist to epinephrin, stimulating an opposing system of nerves. This antagonism of action on the heart, bloodvessels, bronchi, and gastro-intestinal tract is obvious. Epinephrin increases the reflexes and produces a sensation akin to excitement in some subjects. In 2 patients with increased reflexes, it could be demonstrated that acetyl- β -methylcholin depressed reflex activity. In the first patient the biceps and triceps jerks were followed by short series of clonic contractions while striking over the brachial plexus resulted in a twitch of the hand. About an hour after the subject had taken 1 gm. of acetyl- β -methylcholin by mouth, while the flush was present, the clonic contractions did not follow the tendon reflexes, and the brachial plexus response could not be elicited. After atropin the original condition promptly returned. In another case the abdominal reflexes could always be elicited by a stroke which traveled between two marked spots in $\frac{1}{2}$ second, timed by a metronome. After a similar dose these reflexes could be elicited only very infrequently by this procedure. When the effect of the drug had passed off the original condition was restored. But in two acute spinal cats prepared by Dr. Grayson McCouch, acetyl- β -methylcholin could not be demonstrated to have any significant effect on the threshold of the flexion reflex.

We have no evidence that the effect of epinephrin on the basal metabolic rate and blood sugar is opposed by acetyl- β -methylcholin.

We have had no opportunity to test the drug's action on the rarer types of cardiac arrhythmia, nor have we made an adequate study

of the effect of its prolonged administration in cases of hypertension; what little evidence we have is not encouraging.

No evidence has been obtained to indicate that the drug is dangerous when administered in the manner and dosage described. It has been given to very sick people. However, its action after subcutaneous injection is so quick and vigorous that we prepare our subjects for what is coming. We tell them that the injection will cause a sudden sensation of warmth in the face, that it may make them breathe hard for a minute, and that this will be followed by sweating and a flow of saliva. The injections are always given with the subject lying down. We have a syringe containing atropin sulphate gr. 1/50 (1.2 mg.) ready at hand. As atropin, given intravenously, would abolish the action of acetyl- β -methylcholin almost immediately, we advise that this precaution be continued. If the drug is given by mouth this is unnecessary. By this route we have given doses up to 4 gm. daily for a prolonged period without the production of uncomfortable or alarming symptoms.

A few untoward effects have been observed. In a patient who had asthmatic attacks infrequently a subcutaneous injection of 20 mg. caused a typical attack. In this case the pulse rate fell from 108 to 60; the flush, instead of being confined to the face and neck, was generalized; the blood pressure, instead of falling, rose from 138/90 to 170/98. Atropin sulphate gr. 1/75 (0.9 mg.) was given subcutaneously and relief began within 2 minutes. Much milder asthmatic attacks have followed the taking of large doses by mouth in patients subject to asthma, and the same occurred in one elderly subject not known to have had asthma. Therefore, it seems proper to recommend caution in giving subcutaneous injections or large doses by mouth to patients who suffer from asthma and other conditions relieved by adrenalin, a physiologic antagonist of the cholins.

Both dyspnea and substernal pain followed the injection of 20 mg. into a patient who had received 1 gm. by mouth a short time before. This was also cut short by atropin.

In 2 patients who had been vomiting the subcutaneous injection of 10, 20 and 40 mg. was followed by vomiting. No other patients have vomited or indeed felt nauseated after subcutaneous administration. The slight epigastric discomfort which some persons complained of after taking the drug by mouth was almost always prevented by administering it in milk.

One subject complained of a disturbance of accommodation after taking 300 mg. by mouth. This passed off within 30 minutes. Some effect on accommodation is to be expected from the pharmacologic properties of the drug, but no other subjects noticed it.

In 1 case of paroxysmal tachycardia in a very sick patient, the subcutaneous administration of the drug caused momentary com-

plete heart block. The large amount of digitalis which this patient had received may well have been a factor in this case. However, a few blocked beats have been demonstrated in other patients during the transition from paroxysmal tachycardia to normal rhythm. Extrasystoles also occurred during this transition. In 1 case coupled beats were found after the administration of large doses by mouth.

Therefore, it is evident that this drug, like all other active drugs, may produce untoward effects against which the physician must be on his guard. But only 3 times in our experience have these effects been severe enough to necessitate their termination by atropin.

The most spectacular action of the drug is the immediate termination of the attacks of paroxysmal tachycardia, of the auricular or supraventricular type. We know of no other drug which will produce this effect. We have evolved a technique for this purpose.

If our experience is typical the great majority of these attacks can be stopped by the drug alone. If this is insufficient, carotid pressure during the drug's action is usually successful. In the prevention of such attacks acetyl- β -methylcholin proved inferior to quinidin in 1 case. We have had no opportunity of testing the effect of the drug on the ventricular type of paroxysmal tachycardia.

In other types of tachycardia, acetyl- β -methylcholin will at times cause slowing. Whether it can be used with benefit to these patients is as yet undecided.

The increased gastro-intestinal tone and peristalsis which followed the exhibition of acetyl- β -methylcholin have caused striking relief in certain cases of abdominal distention.⁷ But the effect on other types of gastro-intestinal dysfunction has not yet been investigated.

Acetyl cholin has been advocated for the treatment of the spastic types of peripheral vascular disease,⁸ and relief of pain following its use in senile arteritis has been reported.⁹ Acetyl- β -methylcholin has a similar vasodilating action, it is much more stable than acetyl cholin and it produces more prolonged effects. It lacks certain undesired side effects produced by the latter drug. Its peripheral vasodilating action in Raynaud's disease and in certain cases of obstructive arterial disease can be easily demonstrated. The patients in which it has been used have been symptomatically relieved and when an attempt was made to substitute an inert solution for one containing the drug they detected it at once. Acetyl- β -methylcholin seems superior to acetyl cholin in every particular for the treatment of these conditions.

Summary. Acetyl- β -methylcholin has been employed in the treatment of certain types of cardiovascular disease. This drug causes effects similar to those following stimulation of the vagus and other parasympathetic nerves. It also causes peripheral vaso-

dilatation. After subcutaneous injection it has a prompt and vigorous action. Given by mouth the effects are much milder.

The untoward effects of the drug are described. They can be immediately abolished by atropin.

Injected subcutaneously, the drug has caused the immediate termination of 24 attacks of paroxysmal tachycardia in 9 patients. In 7 the attacks were of the auricular or supraventricular type, in the other 2 no electrocardiograms were secured. In most of the attacks carotid pressure and other means had been tried unsuccessfully before the drug was given. In a few instances a combination of the drug's action and carotid pressure terminated attacks which could not be stopped by carotid pressure alone. Failure was very infrequent except when the dosage was inadequate. Electrocardiograms showed the transition from the paroxysm to normal rhythm.

The vascular spasm of Raynaud's disease, when excited by mild degrees of cold, was relieved or prevented by the action of the drug administered by mouth. The spasm following exposure to severe cold was but little affected. The discomfort of 3 such patients was in part ameliorated by taking the drug by mouth during cold weather.

The drug repeatedly caused a rise of the skin temperature of the feet in a case of thromboangiitis obliterans. It relieved the pain in certain cases of threatened gangrene from obstructive peripheral vascular disease. But no evidence of a peripheral vasodilator action could be secured in certain other cases of this type.

The drug caused a temporary reduction of blood pressure in most cases of hypertension. In some such cases relief from headache followed the exhibition of the drug. In other apparently similar cases no relief was secured.

In 1 case Cheyne-Stokes respiration was abolished by the drug. Two other patients, in whom spasm of cerebral vessels may have been a factor, reported improvement of headache and vertigo after taking the drug.

The possible utility of acetyl- β -methylcholin in certain other disease conditions is discussed.

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A DIAGNOSTIC TEST FOR INFECTIOUS MONONUCLEOSIS.

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In a recent article¹ the presence of a rather high concentration of heterophil antibodies, demonstrable in the form of sheep cell agglutinins, has been described in the active stages of 4 cases of infectious mononucleosis. Since then tests for heterophil antibodies have been made in over 2000 cases representing various clinical entities, including additional cases of infectious mononucleosis. The diagnostic value of the test has become increasingly evident. In the present report the results of these tests, with a few modifications of the method, are recorded. No attempt is made to review in detail the development of knowledge of heterophil antigens and antibodies, but a few statements relative to the nature of the phenomenon involved seem desirable.

Forssman² observed that emulsions of the tissues (other than blood cells) of the guinea-pig, cat and horse stimulate the production of lysins for sheep red blood corpuscles, just as sheep erythrocytes themselves do when injected into rabbits. Subsequently, the term Forssman antigen or heterophil antigen has been applied to materials which have this property. Apparently the substances which contain the heterophil antigen are widespread throughout the animal kingdom and to a lesser degree among bacteria as evidenced by the ever increasing list of carriers of heterophil antigen.

Comparatively few bacterial species, however, have been investigated as to their content of heterophil antigens. Such antigens have been found in strains of *B. paratyphosus* B, *B. enteritidis* (Gaertner),³ *B. dysenteriae* (Shiga),⁴ a particular strain of *B. lepi-septicus*⁵ and recently in various types of pneumococci.⁶ The nature of these bacterial heterophil antigens is not thoroughly known. Some appear to be identical with those present in sheep cells or guinea-pig kidney, but others differ somewhat. That the heterophil antibodies are distinct from specific bacterial agglutinins and precipitins is well demonstrated by absorption tests. The possible part played by these heterophil antigens in the development of immunity to various diseases has yet to be demonstrated.

Only recently has the Forssman phenomenon found clinical application. Through the work of Davidsolin,^{7,8} Deicher,⁹ Perry and Rhodes,¹⁰ Paul and Bunnell,¹ and others, the presence of hemolysins and agglutinins for sheep cells in low dilutions of supposedly normal human sera have been repeatedly demonstrated. Friedberger and his co-workers¹¹ have shown that there is a definite age distribution

of this heterophil antibody content, which rises from zero at birth to reach a peak at about the 12th year and then falls gradually through subsequent decades. Paul and Bunnell¹ confirmed this finding in a study of 275 hospitalized patients. There is some disagreement among different investigators as to the percentage of individuals who show heterophil agglutinins in a serum dilution of 1 to 4, but there is apparent complete agreement that the titer rarely exceeds 1 to 8 in normal human serum. Following the injection of horse serum, which is a known carrier of heterophil antigen, an increased titer of heterophil antibodies in the blood of patients suffering from horse serum disease was first reported by Davidsohn^{7,8} in 1929. Agglutination titers ranging from 1 to 32 to 1 to 64 were found at the height of this disease or shortly afterward. He concluded from this that an agglutinin titer for sheep cells of 1 to 32 or higher is suggestive of horse serum sickness in the more or less recent past. Ramsdell and Davidsohn¹² in 1930 reported 26 cases, representing various clinical conditions severe enough to occasion hospital residence, on which determinations of sheep cell agglutinins in the serum were made. In none of the cases, except 1 case of severe diabetes mellitus, which was receiving intensive insulin treatment, was an agglutinin titer greater than 1 to 8 found. Paul and Bunnell¹ in 1932, reported a low titer of sheep cell agglutinins in 323 hospitalized patients representing a variety of clinical conditions. With one exception (a fatal case that was classified as possibly aplastic anemia, but may well have been a case of infectious mononucleosis with complicating acute hemorrhagic nephritis similar to those reported by Tidy and Daniel¹³) no appreciable increase in the sheep cell agglutinin titer was found except in cases of serum disease and infectious mononucleosis.

METHODS. The method we have employed in determining the concentration of the heterophil agglutinins for sheep cells in human sera was reported previously.¹ The serum, from 5 to 8 cc. of human blood obtained as for a Wassermann test, is utilized for the procedure. For sake of conformity in results it is important to use a standard type of agglutination tube. We have found a tube 100 mm. in length and 10 mm. in diameter most satisfactory and have used it in all our tests, as a slight effect upon the readings is noticed with varying sized tubes. The use of a 2 per cent suspension of sheep cells is likewise desirable, as a heavier suspension interferes with the agglutination phenomenon.

If the serum is inactivated properly and the procedure carried out as described, there should be no hemolysis in the tubes to confuse the readings. (In serum which contains bile the sheep cells are usually hemolyzed and the tests unsatisfactory.)

RESULTS. The results of the investigation of various clinical conditions here reported are presented in Table 1. It will be seen that the marked increase in heterophil agglutinins for sheep cells previously reported in infectious mononucleosis has not been encountered in other conditions. In determinations that we have made

on over 2000 individuals, the presence of a consistently low titer is outstanding. In Table 1 the range of agglutinin titers of 437 hospitalized cases representing 76 clinical conditions, including 22 cases of serum disease but excluding the 15 cases of infectious mononucleosis, is shown. In addition Table 2 includes the range of titers found on testing 1600 sera obtained from the Wassermann laboratory. These are arranged in groups according to titer, as diagnoses and ages were not available.

TABLE 1.—SHEEP CELL AGGLUTININS IN MISCELLANEOUS CONDITIONS.

Clinical conditions in groups.	No. of cases.	Range of titer.	Dilutions of patient's serum.							
			$\frac{1}{2}$	$\frac{1}{4}$	$\frac{1}{8}$	$\frac{1}{16}$	$\frac{1}{32}$	$\frac{1}{64}$	$\frac{1}{128}$	
Normals	36	Max. Min.	++ —	+ —	+ —	± —	— —	— —	— —	
Psychosis, toxemia preg., normal preg., metal poisoning	28	Max. Min.	+ —	+ —	± —	— —	— —	— —	— —	
Fractures, burns, myositis	18	Max. Min.	+ —	+ —	± —	— —	— —	— —	— —	
Obesity, gen. arteriosclerosis, diabetes, malnutrition, acute and chronic nephritis, rickets	27	Max. Min.	+ —	+ —	+ —	— —	— —	— —	— —	
Pyoderma, gonorrhea, pelvic inflammation, ovarian cysts, malignancy, etc.	32	Max. Min.	+ —	+ —	± —	— —	— —	— —	— —	
Common cold, grippe, influenza, follicular tonsillitis, otitis media, acute cervical adenitis, acute bronchitis, bronchopneumonia, lobar pneumonia, empyema	48	Max. Min.	++ —	++ —	+ —	± —	— —	— —	— —	
Bronchial asthma, pulmonary tuberculosis, erythema nodosum	33	Max. Min.	++ —	++ —	+ —	± —	— —	— —	— —	
Acute rheumatic fever, rheumatic arthritis, rheumatic heart disease	35	Max. Min.	++ ±	+ —	+ —	± —	± —	— —	— —	
Syphilis: Primary, secondary, tertiary and congenital	16	Max. Min.	+ —	+ —	± —	— —	— —	— —	— —	
Erysipelas, scarlet fever, misc. strep. infections, diphtheria, typhoid, measles, chickenpox, pertussis, mumps, meningococcus meningitis, Vincent's angina	89	Max. Min.	++ —	+ —	+ —	± —	— —	— —	— —	
Primary, secondary and aplastic anemia, erythroblastic anemia, purpura hemorrhagica, Banti's disease	26	Max. Min.	+++ —	+++ —	++ —	± —	— —	— —	— —	
Hodgkin's disease, agranulocytosis, acute and chronic—myelogenous and lymphatic leukemia, malignant thymoma, benign lymphadenosis	27	Max. Min.	+ —	+ —	+ —	— —	— —	— —	— —	
Serum disease	22	Max. Min.	+++ +++	+++ ++	+++ ±	+++ —	+++ —	++ —	— —	

In none of the clinical conditions simulating infectious mononucleosis or those with which it might be confused have we been able to demonstrate any appreciable increase in the agglutinin titer. Cases of acute rheumatic fever and rheumatoid arthritis may occasionally show a plus minus agglutination in a titer of 1 to 32 but none higher has been encountered. Vincent's angina and agranulo-

cytic angina show no abnormal increase of heterophil agglutinin titer. Several of the blood dyscrasias, including acute and chronic myelogenous and lymphatic leukemia, likewise show no increase of agglutinins above the normal level. While clinical conditions associated with bacterial etiologic agents show a tendency to a slightly higher titer than is the case in non-bacterial diseases, the increase is small. Furthermore, the degree of agglutination as well as the titer is strikingly less than in infectious mononucleosis. In serum disease following the injection of horse serum, however, there is a distinct rise in the agglutinin titer though not as high as is usually found in infectious mononucleosis. Likewise, the type of agglutination in the cases of serum disease resembles more closely the reaction found in the cases of infectious mononucleosis.

TABLE 2.—SHEEP CELL AGGLUTININS ON 1600 INDIVIDUAL SERA OBTAINED FROM WASSERMANN LABORATORY ON WHICH DIAGNOSES AND AGES WERE NOT AVAILABLE.

Sera.		No. cases showing various readings in the same titer.	Range of agglutinin titers and readings on individual sera.				
Number.	Per cent.		½.	1.	2.	4.	8.
651	40.7	651	—				
		264	±				
373	23.3	104	+				
		5	++				
		50	±	±			
355	22.2	210	+	±			
		76	+	+			
		19	++	+			
		19	+	±	±		
		53	+	+	±		
144	9.0	6	+	+	+		
		30	++	+	±		
		22	++	+	+		
		14	++	++	+		
		5	+	+	±	±	
		24	+	+	+	±	
		5	+	+	+	+	
64	4.0	3	++	+	±	±	
		8	++	+	+	±	
		13	++	++	+	±	
		3	++	++	+	+	
		3	++	++	++	±	
13	0.8	5	+	+	+	±	±
		8	++	+	+	±	±

In sharp contrast to the findings listed in Tables 1 and 2 are the observations on 15 cases of infectious mononucleosis presented in Table 3. These cases can be classified, on the basis of duration of symptoms, into two groups, the acute cases usually more severe and generally presenting a more pronounced increase in the agglutinin titer for sheep cells, and the subacute cases which run a more prolonged course and show an agglutinin titer not greater than 1 to 128 and usually only 1 to 64. The duration of the acute case is usually 14 to 21 days, while the course of the subacute cases is prolonged for a month or more. Though there is considerable variation in the

TABLE 3.—SHEEP CELL AGGLUTININS IN INFECTIOUS MONONUCLEOSIS.

No.	Type of case.	Age.	Stage of disease serum was obtained.	Duration of illness.
1	Acute	22	7th day 13th day 11 months later	13 days
2	Acute	21	10th day 19th day 4 months later	21 days
3	Acute	25	9th day	16 days
4	Subacute	16	6 months before 10th day 16th day 20th day 1 month later	30 days
5	Subacute	21	At onset 14th day 21st day 28th day	31 days
6	Subacute	25	14th day	30 days?
7	Acute	15	7th day 10th day 18th day	21 days
8	Acute	45	7th day	?
9	Acute	19	6th day 14th day	14 days
10	Acute	23	5th day 10th day 22d day	22 days
11	Acute	20	1th day 4 weeks after onset	18 days
12	Acute	20	14th day	20 days
13	Acute	20	10th day	?
14	Acute	20	4th day	16 days
15	Acute	21	21st day	22 days

agglutinin titer in the group of acute cases, they tend to show a higher titer than the subacute cases. The height of the agglutinin response is fairly well correlated with the severity of the illness and distinctly related to the stage of the disease in which the serum for the test is obtained. This relationship and also the relationship of the associated pathologic lymphocytosis can be better understood by a study of the following case report and graphic presentation of the course of the disease.

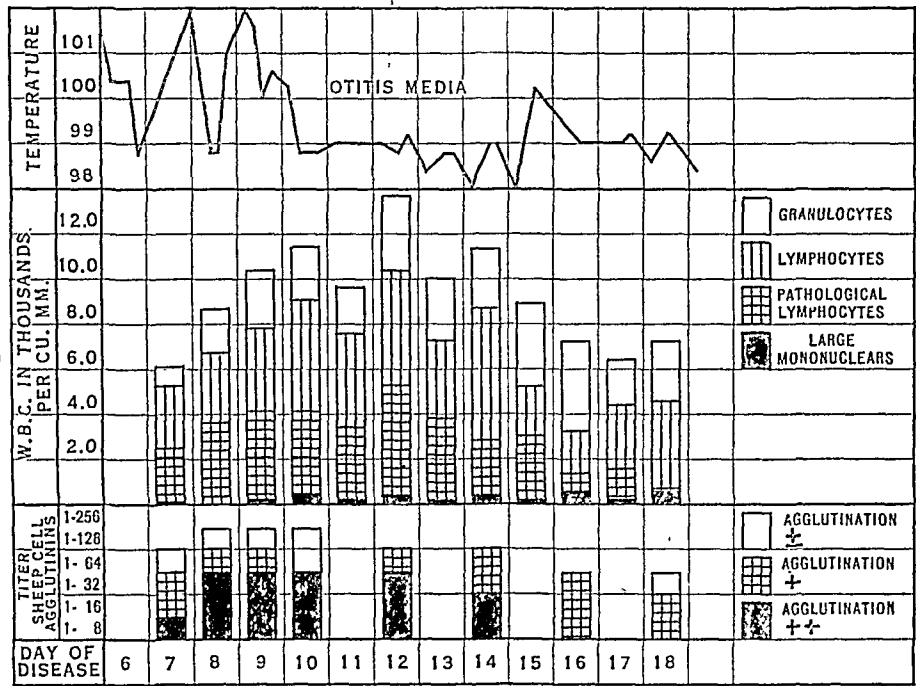


FIG. 1.—Case 7. Infectious mononucleosis.

Case Report. J. W. (Case 7, Table 3), a white American schoolboy, aged 15 years, was admitted to the New Haven Hospital on the evening of December 9, 1931, complaining of fever and dull pain in the right lower quadrant.

He gave a previous history of lassitude, drowsiness, anorexia, slight pain about the umbilicus and fever of about 5 days' duration. Twelve hours after administration of a dose of citrate of magnesia he began to complain of a severe dull pain in the lower abdomen which later localized in right lower quadrant and brought about his hospitalization for acute appendicitis.

On admission the patient's temperature was 101° F. The throat was slightly injected and small ulcerative areas were present on the surface of the enlarged lingual tonsil. The tonsillar fossæ were clear. There was a moderate painless enlargement of the cervical, axillary and inguinal lymph nodes, which were discrete and moderately firm. The liver and spleen were not palpable. There was slight tenderness on deep pressure in both lower quadrants without muscle spasm. The total leukocyte count on December 10, 1931, was 5500, with 58 per cent lymphoid cells and 1 per cent mononuclears. The throat culture showed an essentially normal mouth flora. A stained smear from the ulcerative areas on the lingual tonsil showed numer-

ous diphtheroids and a moderate number of fusiform bacilli with a rare spirillum. Kahn and Widal tests were negative. From a culture of the blood in Savita broth a few diphtheroid-like organisms were isolated after 7 days' incubation. A stool culture was negative for pathogenic organisms.

On December 11, 1932, the patient had a spontaneous epistaxis, the adenopathy had become more pronounced and the spleen was easily palpable, 2 cm. below the costal margin. The leukocyte count at this time was 6100, with 85 per cent lymphoid cells and 3 per cent large mononuclears. Forty-two per cent of the lymphoid cells were typical pathologic lymphocytes which have been so well described by Downey and McKinley,¹⁴ the cells in this case corresponding closely to their so-called Type I. Sheep cell agglutinins at this stage were determined for the first time and found to be present in a titer of 1 to 128. The temperature remained at an elevated level with irregular swings for 5 days following admission. During this time bilateral otitis media developed. The patient's course was otherwise uneventful and at time of discharge a notable decrease in the adenopathy had occurred and the spleen was no longer palpable. The course of the sheep cell agglutinin titer and the progressive change in the blood picture is shown in Fig. 1.

It is of interest to note that the development of the heterophil agglutinins for sheep cells runs parallel to the pathologic lymphocytosis. With the decrease in the agglutinin titer there is a disappearance of the pathologic lymphocytes from the peripheral blood. An absolute lymphocytosis, however, composed of normal lymphocytes, may persist for months. The increase in the total leukocyte count at the height of the disease is apparently due entirely to the increase in the number of pathologic lymphocytes.

Summary. We have employed the sheep cell agglutinin test in over 2000 cases representing 76 clinical conditions. With the exception previously noted, namely, serum disease, we have been unable to demonstrate an appreciable increase of heterophil agglutinins for sheep cells in the sera above the normal dilution of 1 to 8. In 15 cases of infectious mononucleosis we have found a consistent increase in all cases. The titers, ranging from 1 to 64 to 1 to 4096, apparently depended to a considerable extent upon the stage of the disease at which the serum was obtained and upon the severity of the illness. None of the common conditions manifesting a similar clinical picture such as acute adenitis, tuberculous or syphilitic adenitis, Hodgkin's disease, acute or chronic lymphatic or myelogenous leukemia, aplastic anemia, purpura hemorrhagica, agranulocytic angina or Vincent's angina, has shown an increase in heterophil agglutinin titer.

Conclusions. In view of these findings it seems justifiable to accept the test for heterophil agglutinins for sheep cells as a valuable diagnostic procedure in differentiating infectious mononucleosis from a number of clinical conditions of a far more serious nature.

Cases presenting a suggestive clinical and blood picture whose blood serum shows an agglutination for sheep cells in a dilution of at least 1 to 64 can apparently safely be diagnosed as infectious mononucleosis, and a favorable prognosis given.

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AN INSTANCE OF LYMPHATIC LEUKEMIA FOLLOWING BENZOL POISONING.

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(From the Department of Medicine.)

THIS rather remarkable circumstance of a patient under treatment and observation for chronic benzol poisoning, gradually developing the picture of a full-blown leukemia, is of sufficient interest to merit its report in essential detail.

Case Report. A white male, aged 58 years, employed by a can company, was first seen May 21, 1924, complaining of weakness, dizziness, dyspnea and "a puffing noise in the head." History disclosed that his work was to "truck" can ends from the foot of a conveyor to the warehouse. The can ends, rimmed with a solution of rubber in benzol, were delivered to him by a conveyor, the benzol evaporating from the rubber mixture "en route."

He first noted weakness and dizziness April 4. On May 1, weakness in the lower extremities forced him to stop work and consult his family physician who found his "blood thin," administering "iron" injections and "pills" by mouth. There was no past history of infections except for two attacks of "chills and fever" lasting 2 weeks, disappearing without special medication, 8 years and 5 years before the present illness. There was no history of anemia or previous weakness.

Physical examination showed a short, obese, pale man with a sallow tint to skin. Several teeth missing. Moderate degree of peridentosis present. Palpable posterior cervical and inguinal nodes. Blood pressure: systolic, 130; diastolic, 80. Heart slightly enlarged to the left by percussion. The first heart sound was feeble over lower precordium, accompanied by a soft, blowing systolic murmur heard best over the pulmonic area. Chest showed impaired resonance at the right base, with harsh breath sounds but no râles at this area. Abdomen protuberant, rounded. The edge of the liver was palpable 3 cm. below the costal border, slightly tender. Spleen not felt. Over skin of trunk, extensor surface of arms, and over both lower extremities

below the knees were small, dull, red to purplish-red spots from 0.5 mm. to 1 mm. in diameter. They do not fade on pressure and represent typical purpuric areas. The "tourniquet test" is positive. The knee jerks are sluggish. No sensory disturbances made out.

The blood studies at this time showed hemoglobin 50 per cent (Newcomer); red cells, 1,530,000; white cells, 8100 per c.mm. Differential: neutrophils, 62; lymphocytes, 32; monocytes, 6 per cent. Platelet count, 68,000 (Reese and Ecker¹). The red cells showed anisocytosis, a few large red cells, some showing polychromatophilia.

The author had seen 4 cases of typical benzol poisoning from the same plant during the previous year. Therefore, with the history of exposure and the blood findings detailed above, with the spleen not palpable and no immature white cells appearing on any of the smears, a diagnosis of benzol poisoning was made.

Clinical Course. On June 4, 2 weeks after the first visit, hemorrhage from the nose began. His red and white cell counts began to decrease. Platelets were 74,000. He was admitted to a hospital and received a transfusion of 700 cc. whole blood. Within 3 days the nasal bleeding ceased and after 1 week he was able to leave the hospital.

On July 7, he began reporting to the author for observation and treatment. Three times per week intravenous injections of sodium cacodylate were administered, 1 cc. of a 19 per cent solution. In addition he took Bland's powder, 0.3 gm. after each meal. On September 9, nasal bleeding again occurred; also a pigmented papular mole 0.5 cm. in diameter on the back of his chest continually oozed blood. He was readmitted to the hospital and transfused with 600 cc. whole blood. After 1 week, bleeding having ceased, he was discharged from the hospital. Improvement progressed slowly in red cell count and hemoglobin, but the platelets remained low in number. The accompanying chart of his blood-counts, in chronological order, show his progress. By the end of March, 1925, he was allowed to take up light work about the exterior of the plant. In June, the notes state, "Doing light work and progressing favorably." The platelets lagged behind the other formed elements of the blood. The red cells showed central pallor and anisocytosis. By January, 1926, the platelets had reached 116,000; the red cells and hemoglobin seemed to have reached a new level of blood production, considerably lower than the normal standard but sufficient to maintain him at a comfortable working status. His work called for very little actual physical exertion.

On March 19, 1926, it was noted that his white count had risen to 13,200, with polymorphonuclear neutrophils, 36; eosinophils, 1; lymphocytes, 56; monocytes, 6; neutrophilic myelocytes, 1 per cent. The table shows the blood counts as the leukemia progressed and accompanying charts illustrate in graphic form the blood picture from early symptoms of the benzol poisoning to his demise from leukemia.

He remained at light work throughout 1926, the white cells gradually rising and hemoglobin and red cells gradually falling. By January 22, 1927, the white cell count had risen to 49,500, with polymorphonuclear neutrophils, 9; eosinophils, 1; lymphocytes, 89; monocytes, 1 per cent. Many of the lymphocytes now were somewhat larger than the normal lymphocyte with a paler staining, less dense nucleus than one sees in a normal smear. They were not definitely lymphoblasts, so are included under the designation lymphocytes. McJunkin's oxydase stain on January 22, 1927, showed granular cells 16, non-granular 84 per cent. Patient stated he felt well except for slight weakness and dyspnea and he did not wish to give up his work. On July 8, on account of weakness and dyspnea he was forced to stop work. On December 16, the white cell count was 103,300 with neutrophils, 4; lymphocytes, 92; lymphoblasts, 3; neutrophilic myelocytes, 1 per cent.

The hemoglobin was 39 per cent, and red blood cells 1,520,000. Daily doses of 6 vials Lilly's Liver Extract No. 343 were tried. The reticulocyte rise was not above 1 per cent. On February 1, 1928, he was readmitted to the hospital and on February 16, death occurred. The clinical diagnosis was lymphatic leukemia.

TABLE 1.—WHITE BLOOD CELL AND PLATELET COUNTS EXTENDING OVER 3 YEARS, 8½ MONTHS.

Date.	Total white count per c.mm.	Neutrophils, per cent.	Basophils, per cent.	Eosinophils, per cent.	Lympho. per cent.	Mono. per cent.	Platelets in thousands per c.mm.
5/21/24 . . .	8,100	62	32	6	
6/ 4/24 . . .	4,600	50	..	3	41	6	74
7/ 7/24 . . .	3,400	32	..	1	59	8	64
8/25/24 . . .	4,400	70	1	..	22	7	72
9/30/24 . . .	7,120	50	..	1	40	9	68
11/11/24 . . .	5,300	68	..	1	25	6	74
12/10/24 . . .	8,200	61	32	7	68
2/ 6/25 . . .	7,400	59	..	1	37	3	70
3/17/25 . . .	5,000	45	53	2	72
5/18/25 . . .	8,320	64	1	1	31	3	88
8/24/25 . . .	9,300	58	37	5	114
1/12/26 . . .	7,800	58	38	4	116
3/19/26 . . .	13,200	36 (1)	..	1	56	6	74
3/30/26 . . .	12,400	34	57	9	
4/16/26 . . .	14,000	46	1	1	43	9	68
6/22/26 . . .	16,920	52	43	5	88
1/10/27 . . .	49,500	9	..	1	89	1	160
3/21/27 . . .	42,400	28	71	1	120
4/18/27 . . .	56,000	17	81	2	100
5/ 9/27 . . .	58,000	16	82	2	112
5/25/27 . . .	55,000	16	83	1	76
6/ 9/27 . . .	64,400	12	87	1	132
7/ 8/27 . . .	63,000	8	92	..	66
7/21/27 . . .	44,400	6	90	4	
7/30/27 . . .	70,600	12	88	..	86
9/22/27 . . .	79,400	5	92	3	54
10/31/27 . . .	69,500	9	89	2	40
12/ 8/27 . . .	71,600	3	1	..	93	3	34
12/16/27 . . .	108,300	4 (1)	92 (3)		
1/ 4/28 . . .	89,000	2	95	3	30
1/20/28 . . .	94,000	3 (1)	94	2	50
2/ 1/28 . . .	108,000	4	96	..	60
2/13/28 . . .	140,000	2	98	..	34

() = Immature cells.

Postmortem Examination. (By Drs. G. Y. Rusk and S. R. Mettier, 6 hours after death). The body was well developed and moderately obese. The skin and mucous membranes were pale. The cervical, axillary, inguinal, mediastinal and mesenteric lymph nodes were moderately enlarged. The blood, as it escaped from the various severed vessels, appeared thin and watery. The *heart* was normal except for petechial hemorrhages on the pericardium and endocardium. Both lungs contained small patches of bronchopneumonia and the larger bronchi were filled with a purulent exudate. The *liver* was enlarged, and minute nodules of leukemic infiltration could be seen with ease. The *spleen* weighed 290 gm. It was red, pulpy, and the Malpighian corpuscles appeared enlarged. The kidneys had a combined weight of 380 gm. Scattered throughout the cortex and

medulla of the kidney were numerous small white nodules. The bone marrow in the upper third of the right femur appeared firm, yellowish-white in color, and contained scattered red hyperplastic areas.

Microscopic Examination. The representative specimens of lymph nodes from the various chains were stained with eosin and methylene blue, and showed an absence of normal architecture. There was no differentiation between the follicular and medullary portions. No germinal centers could be seen. There was a general overgrowth of tissue by a type of cell slightly larger than the usual lymphocyte, and which contained a thin rim of protoplasm. The nuclei as a rule were round, clear and did not stain as deeply as normal lymphocytes. Some of these cells showed a slight nuclear indentation. Among some of these cells could be seen an occasional one in which the nucleus appeared to be undergoing an amitotic division. Sprinkled in between these cells could be seen numerous red blood cells, and some of these appeared similar to the normoblast.

Bone-marrow (Giemsa) showed a moderate number of fat-cells. The interstices between the fat-cells were infiltrated by large numbers of cells similar to those described as seen in the lymph-node. Some of these areas were large and completely obliterated the fatty tissue. Oxydase stain showed very few myelocytes. Only an occasional small focus of red blood cell formation could be identified.

Heart. In the pericardial fat there were definite small cellular accumulations, but none in the heart muscle. These cells again were similar to those described above. In the coronary vessels large numbers of leukemic cells could be seen.

Spleen. The Malpighian corpuscles were irregular in size and shape, but in general were enlarged. The pulp was markedly increased in cellularity, the predominating cell being the lymphocyte. Among these cells was an occasional nucleus undergoing amitotic division.

Liver. There were numerous foci of leukemic infiltrates which were, for the most part, periportal in distribution. There was a considerable amount of hemosiderosis.

Kidneys. Small aggregations of leukemic cells were found between the tubules; an occasional cell could be seen undergoing amitotic division.

Anatomic Diagnosis. Lymphatic leukemia, chronic. Generalized lymphadenopathy, especially in mediastinal retroperitoneal and mesenteric nodes. Splenomegaly, 290 gm. Leukemic infiltration of liver and kidneys. Petechial hemorrhages in epicardium. Secondary anemia. Bronchopneumonia and purulent bronchitis.

The accompanying microphotographs of actual blood smears and of tissue-sections of lymph nodes and bone-marrow show numerous lymphatic cells in the process of direct nuclear division (amitosis). It will be seen in the accompanying microphotographic figures that this feature of amitosis is particularly striking.

Benzol and Leukemia. Three important questions are suggested by a study of the clinical data and autopsy material of this patient:

1. What effect does benzol have on lymphatic tissue?
2. Is it not possible for benzol, like other well known hemopoietic irritants, to upset the hemopoietic balance between cell growth and destruction, giving rise to lymphoid hyperplasia?
3. Does this lymphoid hyperplasia always stop just short of leukemia, or can it, under prolonged irritation or in susceptible individuals, progress to lymphatic leukemia?

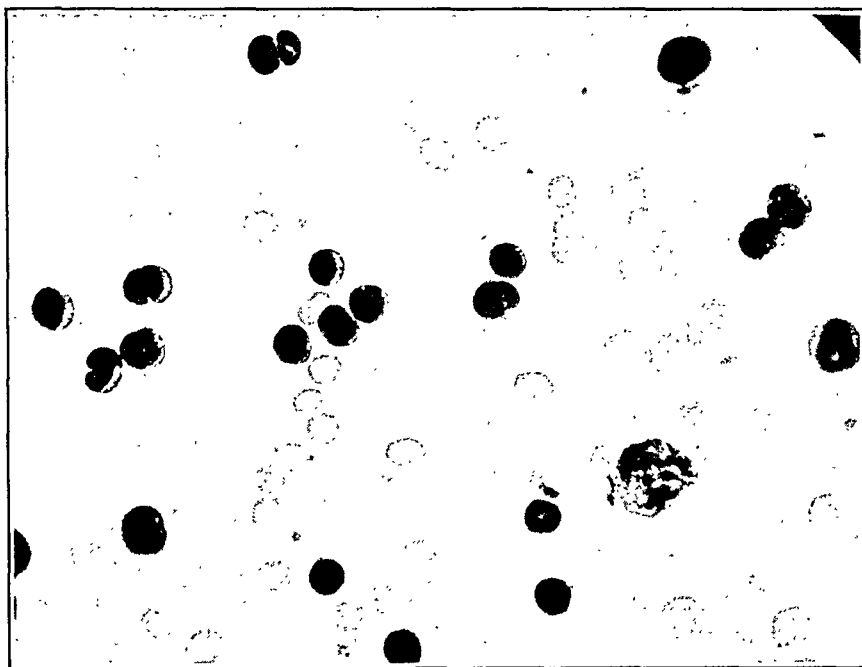


FIG. 1.—Blood film (Jenner-Giemsa stain). Showing direct division of cells.

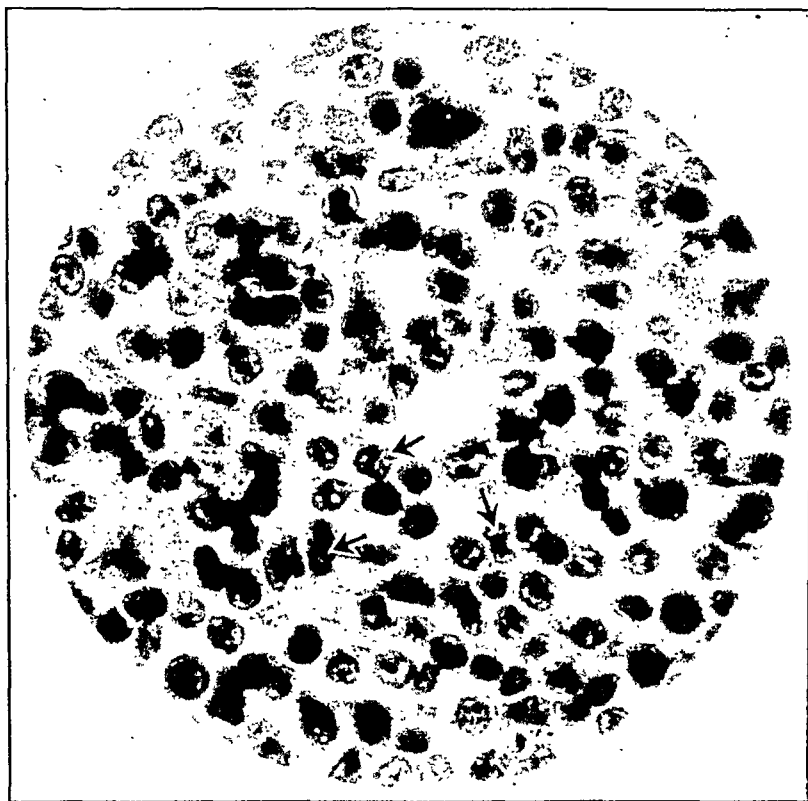


FIG. 2.—Bone marrow.

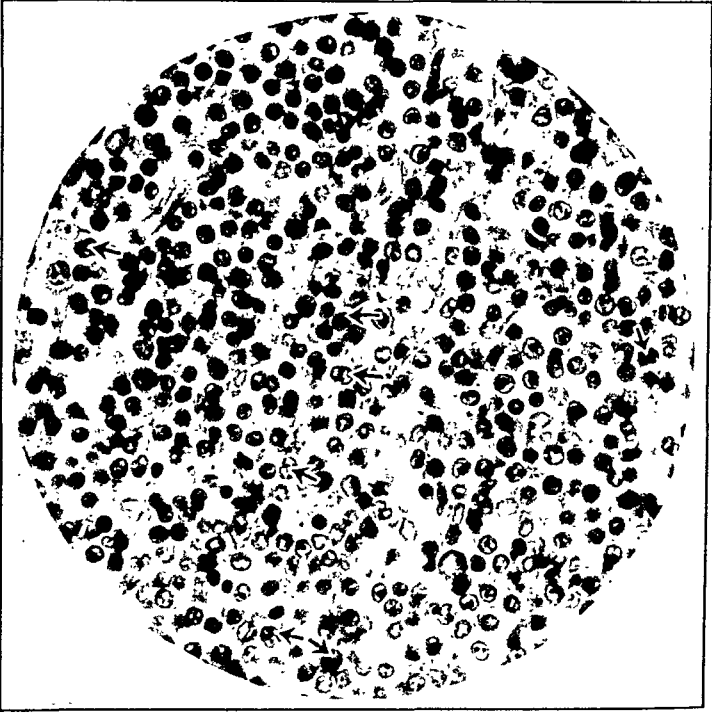


FIG. 3.—Lymph node.

Among the experimental work on the action of benzol on lymphatic tissue, G. O. E. Lignac² in 1928 reported the results of injecting mice with from 25 to 30 injections of benzol (0.1 cc. of 0.3 cc. benzol in 10 cc. olive oil). He concluded: "All the symptoms of hyperplasia developed. After a time the spleen, which was at first hypertrophied, decreased in size. No animals showed lymphatic leukemia, only hyperplasia. Up to the present time, I have not succeeded in producing lymphatic leukemia." He further states, "The experiments cited are not numerous but are important in connection with work with leukemia. In the mice the growth is not ordinary hyperplasia, but should be considered as a tumorous growth similar to leukemia. Precursor cells show spontaneous growth from numerous centers, in 1 case breaking the liver capsule. It is a real tumor of precursors of white blood cells. The immature or undifferentiated cells suggest acute leukemia. Development of tumor may, or may not, be accompanied by a leukemic blood picture. No one knows what factors cause an overflow of leukocytes into the blood stream."

In connection with hemopoietic irritants some interesting experimental work by Murphy and Sturm³ appears to have a bearing. They subjected mice, rats and guinea pigs to dry heat at temperatures of from 55° to 65° C. Short exposures of about 5 minutes were carried out and white counts were made at intervals over a 3 weeks' period. There was an immediate drop in both neutrophils and lymphocytes which averaged about 3000 cells per c.mm. Seven days after the heating, there was an increase of from 5000 to 10,000 cells per c.mm., the increase being almost entirely in the lymphocytes. Fourteen days after heating, the lymphocytes had increased to from 12,000 to 14,000 per c.mm. above the original counts. The neutrophils remained low and did not begin to increase until about 3 weeks after heating. The lymphocytes were still high, but were beginning to drop back toward normal. Both the large and small lymphocytes were healthy-looking, and did not differ in appearance from those of the normal animal. At from 6 to 10 days after heating, several lymphocytes were noted that appeared to be in process of amitotic division. Every stage of this division could be seen. In some instances from 4 to 5 cells in process of division could be seen in one microscopic field. The microphotographs of these cells, accompanying their paper, bear a striking resemblance to the microphotographs showing amitotic division in this article.

Nakahara,⁴ investigating the source of lymphocytosis induced by heat, found that the first change in the spleen and the lymph glands was widespread degeneration of the lymphoid elements. Within 48 hours this was followed by activity of the so-called "germinal centers" with an overproduction of lymphocytes, the spleen and lymph glands becoming larger than normal. There was a marked increase of mitotic figures in the lymphocytes of the germinal centers following the general necrosis.

CHART I.

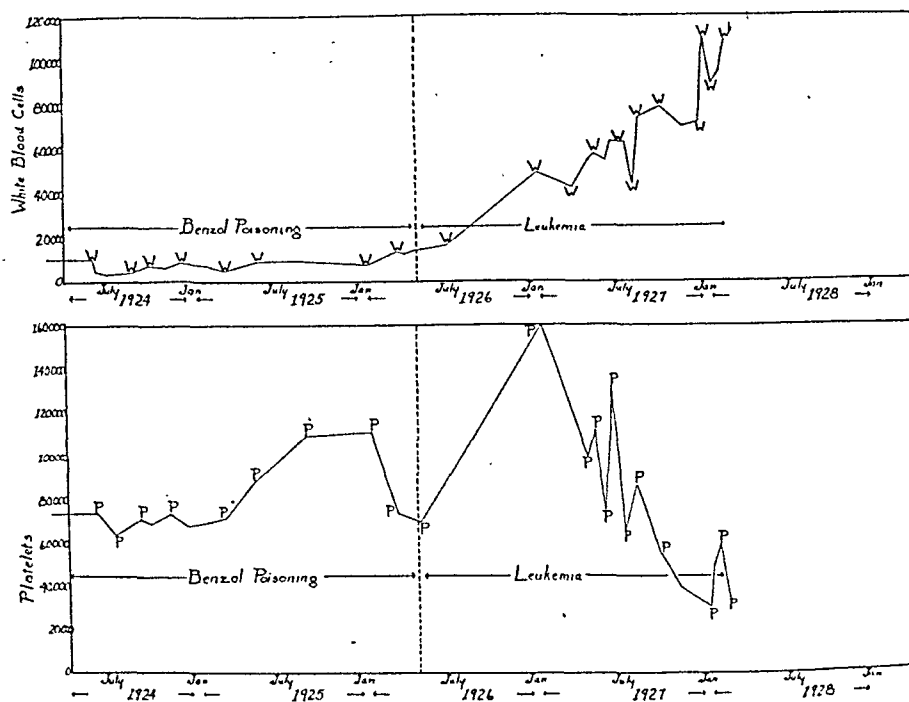
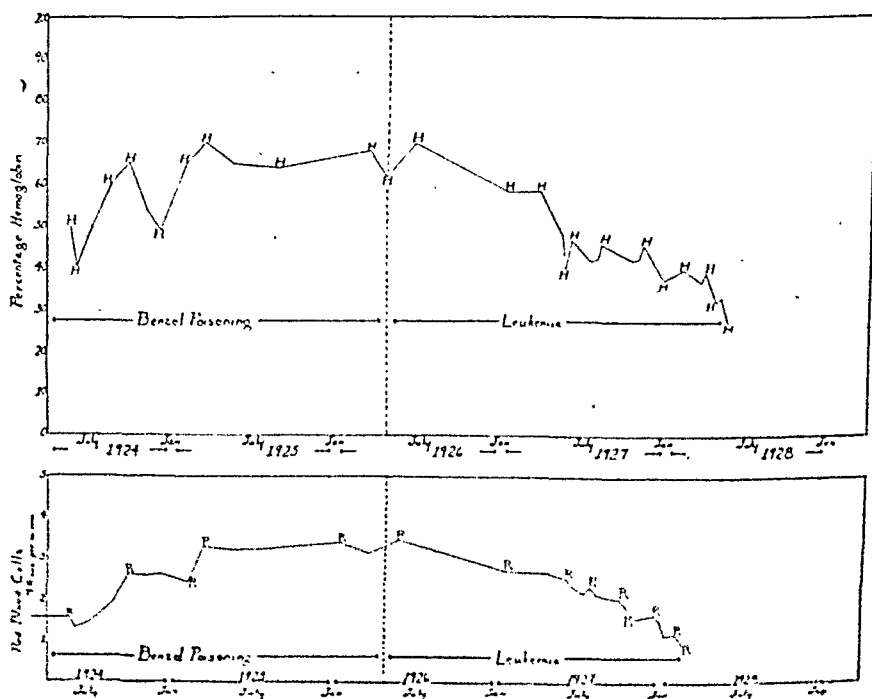


CHART II.



These experiments suggest that benzol may act on lymphatic tissue in a similar manner to dry heat, causing first destruction, then a compensatory hyperplasia, exceeding what we recognize as normal limits. One wonders if under repeated stimuli of this type the balance between orderly production and destruction of lymphocytes might not be upset, resulting eventually in a leukemia. It will be recalled in this connection that Yamagiwa and Itchikawa⁵ succeeded in producing tar cancers in rabbits, after other experimenters had failed, by carrying on the chronic irritation over a sufficiently long period of time and by using rabbits instead of less susceptible laboratory animals.

The Action of Chemicals, Toxins and Radiation on Lymphatic Tissue. In connection with chemicals, arsenic has long been of interest because of its known power of influencing hemopoietic tissue. Isaacs⁶ has studied its effect on red cells, but no mention is made of its action on lymphocytes. He concluded that arsenic acts as a depressor of the bone-marrow causing a decreased production of young red blood cells. When arsenic is stopped, the bone-marrow responds once more with an increase in the rate of maturation of the erythroblastic tissue and an increased production of young red blood cells. In 1929, Baldridge, Rohner and Hausmann,⁷ in a report on infectious mononucleosis, mention in their series 6 cases developing a mononucleosis while under antiluetic treatment. In 1925, White⁸ reported a severe case of infectious mononucleosis developing under antiluetic treatment. The author, in 1925 (unreported), studied a case presenting a clinical picture of infectious mononucleosis with a severe Vincent's infection of the buccal cavity, developing after neoarsphenamin administered for a luetic infection.

It has been considered by some writers (Farley⁹) that the benzol ring in arsphenamin and its derivatives may be responsible, along with arsenic, for hemopoietic tissue damage. The toxins of certain acute infections have long been considered to be a cause of leukemoid blood-pictures, and some writers, as Sternberg,¹⁰ believe acute leukemia is an infection. Cabot¹¹ reports leukemoid blood-pictures following lymphangitis, furunculosis, acute streptococcus tonsillitis and cervical adenitis. Herz¹² mentions cases of infection with a blood-picture simulating lymphatic leukemia. Türk (quoted by Herz) believes there is a relationship between "lymphatic reaction" and lymphatic leukemia. Marchand¹³ presents a case of severe sepsis with bone-marrow exhaustion, and a picture of lymphoid hyperplasia. This last instance is a situation somewhat comparable to the case under consideration where benzol exhausting the bone-marrow is followed by lymphoid hyperplasia and lymphatic leukemia.

The effect of Roentgen rays and radium on hemopoietic tissue has not as yet been well worked out. This is due to the length of

time necessary and the number of factors, such as dosage and susceptibility, that must be controlled in such experimental work. There are cases reported of leukemia and also of aplastic anemia resembling pernicious anemia in workers exposed to Roentgen ray and radium. Emile-Weil¹⁴ reported 2 cases, engineers working in the same laboratory with radioactive material. One died with pernicious anemia and the other with myelogenous leukemia. He quotes other reports in the literature, mentioning deaths from lymphatic leukemia. Farley,¹⁵ commenting in *Medicine* (1928) on Emile-Weil's report states, "In view of the undoubted production of aplastic anemia by the action of rays on the bone-marrow, it is not surprising that the production of a myelogenous type of leukemia by rays should be reported, but the production of lymphatic leukemia by such means should not be credited without very close scrutiny."

It seems to me that Farley's comment refers to the action of rays on the bone-marrow, but if radiation of the marrow can bring about aplastic anemia and myelogenous leukemia, it would seem as if these same rays, acting on lymphatic tissue, much more easily influenced by radiation, might produce a lymphatic leukemia. The bone-marrow is only a portion of the hemopoietic system, all portions of which must be closely interdependent. The exact mechanism of the production of a leukemia is unknown in either case. One can speculate that it is chronic irritation applied to cells whose function is that of growth primarily. The response of cells to irritation is division and growth, or death of the cell.

Experimental work carried on at the Rockefeller Institute¹⁶ tends to show that with a certain dose of Roentgen-ray, a lymphocytosis similar to that produced by heat can be brought about. Blood counts after the treatment described show a lymphocyte change characterized by an initial fall, followed by a marked rise.

Discussion. The data presented in this case are not regarded as furnishing definite proof that benzol caused the lymphatic leukemia. The suggestion to which the evidence points is that the benzol exposure acted as an irritant and destructive agent to the hemopoietic system, upsetting the balance between lymphocyte production and destruction, resulting in lymphatic leukemia. The action of the benzol in destroying erythropoietic and leukopoietic tissue caused a stimulus for regeneration of these two types of tissue, located chiefly in the bone-marrow. The damaged marrow could only respond to a limited extent, producing a red cell and granulocyte response at a level which remained at first below the former normal level. A considerable stimulus for regeneration must operate on the hemopoietic tissue as a whole in these cases of marrow damage. In an individual with a labile lymphatic apparatus, as this individual under consideration appeared to have, the lymphatic response may be unusual and carry on to a leukemic state. This patient was a short, obese individual, who, at age 58, had hyper-

trophied tonsillar tissue, and looked like the typical, so-called "lymphatic" type. Individual susceptibility must be an important factor in determining the response of hemopoietic tissue to various types of irritative and destructive stimuli.

Conclusions. 1. A case of benzol poisoning is presented in which the patient recovered for a time, settling to a new and lower level of blood cell production, then gradually passing into a true, autopsy verified status of lymphatic leukemia with a fatal termination.

2. Instances are drawn from the literature suggesting that benzol, like other agents destructive to hemopoietic tissue, may upset the balance of orderly blood cell production and destruction, bringing about a tissue-environment favorable to the production of lymphatic leukemia.

3. Attention is directed to the presence of direct division of the nucleus, both in many lymphatic cells in the blood stream and in lymphatic tissue cells in lymph nodes and bone-marrow.

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THE ADVANTAGES OF INTRAMUSCULAR INJECTIONS OF A SOLUTION OF LIVER EXTRACT IN THE TREATMENT OF PERNICIOUS ANEMIA.

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THE desirability of large doses of liver in the treatment of the patient with pernicious anemia as originally advised by Minot and Murphy¹ has become almost universally recognized during 8 years

of use in thousands of patients. The development of a fraction of liver for oral administration by Cohn and his associates² has made it possible for many persons to consume adequate amounts with less difficulty than when whole liver is used. Liver fractions and other substitutes for liver, to be ingested, have shown no other advantage than this over the use of whole liver, and are uniformly more expensive to use. The first solution of liver extract prepared for intravenous injection,³ although potent, was not practical for general use. The development of a concentrated solution for use by intramuscular injection has made the problem of adequate dosage more simple and more certain than it has ever been before.

Early trials, at this hospital, with intramuscular injections of a simple solution of liver extract indicated the practical value of such a method. Following a report⁴ of May 26, 1931, concerning one of the earlier cases treated with this extract, observations in a series of 24 patients who had received intramuscular injections were reported.⁵ The results obtained in the larger group demonstrated conclusively the important and striking effects anticipated as a result of the preliminary work. These results have also been confirmed in this country by several investigators working independently.^{6,7,8,9}

It was obvious that in order to be practical for general use the solution for intramuscular injection must be of such a nature that it could be easily and safely used and of such a concentration and potency that the optimal results should be obtained with the fewest possible injections. This was accomplished by the production of a solution of liver extract of such a concentration that the active substance from 100 gm. of liver was contained in 5 cc. of solution. This preparation,* the first for intramuscular injection to be made available for general use in this country, after acceptance by the Council on Pharmacy and Chemistry of the American Medical Association was further concentrated and certain irritating substances eliminated, so that 3 cc. of solution retained the same potent material as was contained in 5 cc. previously. The potency of this material as determined by its clinical effect may be indicated by comparison with the effect of whole liver, which may best be considered as the standard for potency. It has been estimated from observations made during the maintenance treatment of 81 patients by means of intramuscular injections of Solution of Liver Extract (Lederle) that the contents of a vial (3 cc.) containing active principle from 100 gm. of liver will replace from 30 to 50 times that amount (3000 to 5000 gm.) of whole liver administered by mouth.

The practical efficiency of a concentrated solution of liver extract, when given intramuscularly as observed in the treatment of 101 cases and reported in a previous paper,¹⁰ has led to the following conclusions

* Solution Liver Extract Parenteral—Lederle Laboratories, Inc.

in regard to the advantages of this form of treatment as compared with either the use of whole liver or potent substitutes for administration by mouth or less concentrated solutions for intramuscular use.

1. *Certain Dosage.* The dosage is under absolute control of the physician. Although the treatment may be given by the patient's nurse, the relative infrequency of treatment makes it quite possible and desirable for the physician to do this. In consequence the physician will see the patient at frequent intervals, thereby insuring him of the best results.

2. *Severe Relapse.* Its strikingly rapid effect makes it the treatment of choice for the patient in severe relapse. The first and maximum effects are evident many hours before these effects may be observed following the administration of liver or liver substitutes by mouth. As previously suggested,⁵ it may well replace transfusion in the critically ill patient.

3. *"Resistant" cases.* Because of the ease and certainty of administering adequate amounts of effective substance the intramuscular injection of the concentrated solution is particularly valuable for the treatment of the patient in whom it has been found difficult to maintain an essentially normal condition of the blood. This apparent resistance to satisfactory improvement may be due in some instances, when liver or liver extract is given by mouth, to an inability on the part of the patient to obtain, to take or to utilize an adequate amount of the material in liver which is effective in producing blood.

4. *Combined System Disease.* Since control of the conditions associated with spinal cord or peripheral nerve damage depends primarily upon the utilization of optimal amounts of the active substance in liver, the concentrated solution given intramuscularly is the treatment of choice.

5. *Uncomplicated Pernicious Anemia.* For the patient with uncomplicated pernicious anemia the routine maintenance treatment with intramuscular injections of the concentrated solution of liver extract is an ideal method. The certainty of dosage and the convenience of its use, because of the relative infrequency of administration in this group particularly, is generally appealing to the patient. It has been found¹⁰ that optimal results are to be obtained by injections of the contents of a vial (3 cc.) at intervals varying from 1 to 6 weeks, the average interval being 3 to 4 weeks. The use of intramuscular treatment does not contraindicate a subsequent return to peroral therapy if this be desired.

6. *Economy.* The saving possible through the use of this method of treatment is of especial interest to those patients who must continue treatment throughout life. Not only is the cost of material small in comparison with that of liver or its substitutes for oral use, as previously shown,⁵ but also a saving is almost always pos-

sible, even including the expense of injection. This saving is particularly noticeable with the use of the concentrated solution described by the author,⁵ because of the low cost of the material and the relative infrequency of injection as compared with less concentrated solutions.

7. *Travel.* It is often difficult for the patient travelling to be certain to obtain good liver along the route and the substitutes for ingestion are bulky to carry. Intensive intramuscular therapy prior to the trip will be sufficient for several weeks without further treatment, or a few vials may be easily carried and injected as desired en route.

8. *Mode of Administration.* That the solution must be administered by needle may be considered as a minor disadvantage of this form of treatment compared with peroral therapy, although the relative infrequency of injections made possible through concentration of the solution has minimized this disadvantage.

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CONGENITAL AORTICOVENTRICULAR FISTULA WITH ENGRAFTED ACUTE SUPPURATIVE ENDOCARDITIS.*

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COMMUNICATIONS between the aorta and the right ventricle are rare. The majority reported have been aneurysms of the aortic septum, rupturing into the right ventricle. But 3 cases have been reported of a congenital communication between the aorta and the right ventricle. These are:

* Read before the New York Pathological Society, December 10, 1931, and the Brooklyn Pediatric Society, March 22, 1931.

Rickards,¹ male, aged 30. The right and left anterior aortic valves were congenitally fused. Behind the right half was a large round orifice, with smooth, membranous, funnel-shaped wall, opening into the right ventricle, between healthy pulmonary cusps. Immediately below the same cusp was a circular aperture in the septum with smooth, membranous wall, passing into the conus of the right ventricle.

Charteris,² male, aged 53. Immediately behind the right aortic valve was a rounded opening with firm margin leading into the right ventricle. A patch of endocardial thickening was present on the opposite wall of the right ventricle.

Livingston,³ male, aged 4 months. The aortic valve was bicuspid, the heart was enlarged. At the commencement of the aorta, a communication led into the right heart, opening above and below the tricuspid valve, and partially closed by a part of this valve.

To these we wish to add a fourth case.

Case Report. A. M., male, white child, aged $1\frac{1}{2}$, was hospitalized on January 30, 1931, with complaints of fever, weakness and irritability.

Past History. Patient was a normal, spontaneous, full-term baby. The patient had "frequent attacks of tonsillitis," and had an attack of "grippe" 2 weeks prior to the present illness. There was no history of dyspnea nor cyanosis.

Present Illness. The present illness began 4 days prior to hospitalization with joint pains and pyrexia ranging from 103° to 106° . Acute rheumatic fever was diagnosed and hospitalization ordered.

Examination revealed a very pale and markedly dyspneic male infant. The tonsils were congested, the lungs, abdomen and extremities were negative. The knees and elbow joints only were painful, particularly on motion. There was no redness, heat or swelling.

The heart was enlarged to the right and left. A soft systolic blow, localized to the apex, was present. At the midsternum there was a loud, harsh, flapping-to-and-fro murmur. A rough systolic murmur was present at the pulmonic area, transmitted upward to the left. The second pulmonic sound was not heard. The temperature was 105° ; pulse 160 and weak.

Blood count: red blood cells, 3,100,000; hemoglobin, 60 per cent; white blood cells, 23,000; differential: 87 per cent polymorphonuclears; 13 per cent lymphocytes.

Roentgenologic examination revealed an enlarged cardiac shadow. The child's condition rapidly became worse and he died on the following morning.

The blood culture revealed streptococcus hemolyticus, beta type.

Autopsy Protocol. Autopsy was performed 2 hours postmortem.

The body was that of a well-nourished and developed white male child, weighing 28 pounds, and 36 inches long. The skin and the conjunctivæ were extremely pale; the lips and finger tips were pale and cyanosed. No petechiæ nor hemorrhages were present anywhere.

The pericardium was not adherent to the pleura. The parietal pericardium was dulled, gray and loosely adherent to the visceral layer in 2 places. One area, 1.2 cm. in diameter, was situated on the anterior surface of the left ventricle at its midportion just lateral to the anterior descending branch of the left coronary artery. The other area was 2.5 cm. in diameter, irregularly circular in outline,

and was situated over the base of the pulmonary and aortic conus and the adjacent anterolateral wall of the right ventricle. No free fluid nor blood was present in the pericardial cavity. The left ventricle was moderately hypertrophied, the left auricle was slightly hypertrophied and dilated. The tricuspid, mitral and pulmonic leaflets were intact. The endocardium of all the chambers, except as stated hereafter was smooth and glistening.



FIG. 1.—Heart opened exposing left ventricle and aorta to show bifid aortic valve and aortic opening of fistula. (1) Coronary orifices; (2) aortic opening of aortico-ventricular fistula containing thrombus; (3) anterior aortic valve cusp; (4) posterior aortic valve cusp.

The aortic valve was composed of two cusps, a normal-sized posterior, and an anterior approximately twice the length of the former (Fig. 1). Midway along this cusp was a slight longitudinal bulge of the anterior aortic wall forming a faint ridge, extending into the

sinus of Valsalva, resembling a very imperfect and rudimentary right-left commissure. This anterior cusp was diffusely thickened, firm, and opaque white; its free edge, smooth and covered by an apparently intact endocardium, was somewhat gouged posteriorly; the sinus of Valsalva narrowed here. Both coronary orifices appeared to enter into the same sinus.

Between these orifices was a round aperture 0.6 cm. in diameter and on the same level with them. The edges of this orifice were thickened, indurated and smooth except along the upper border, where there was slight ulceration. This opening led into a fistulous tract which extended through the aorticopulmonary septum, obliquely downward, forward and to the right, to open into the right ventricular cavity immediately beneath the commissure between the right and left posterior pulmonic valve cusps and just below the level of attachment of these cusps. The commissure was slightly widened, the cusps pushed somewhat apart (Fig. 2). This tract narrowed progressively from aorta ventricleward. The lumen of the tract was filled with soft, gray-yellow thrombus, a portion of which projected through the aortic opening into the aortic lumen; the aortic end of the tract was only partially filled with the thrombus. At the ventricular end the thrombus was very firmly adherent to the tract wall; at the aortic end it was a bit more loosely attached. The ventricular opening of the tract had a ragged edge; to the occluding thrombotic material was attached a narrow bit of fibrin which spread onto the ventricular endocardium for about a millimeter in all directions.

Communicating with the tract was an irregular triangular cavity in the posterolateral wall of the right ventricle, 1.2 cm. in length, about 0.4 cm. wide at its base (valveward) and occupying nearly the entire thickness of the wall. This area bulged slightly into the ventricular cavity. The overlying endocardium was dulled; there was no gross ulceration of the endocardium and no attached thrombi.

One-half centimeter distal to the origin of the left subclavian artery, the aorta, previously 2 cm. in diameter, narrowed to 1.4 cm. in diameter for a distance of 0.6 cm., again to become 2 cm. wide more distally.

The foramen ovale and the ductus Botalli were completely occluded.

The kidneys showed a diffuse cloudy swelling and numerous, minute abscesses. The spleen was of the red splenic tumor type. The liver showed a diffuse cloudy swelling. The other organs showed no gross changes.

Microscopic Examination. The sections of the fistulous area were composed of peripheral zone of cardiac musculature, central to which was a zone of granulation tissue bordering the lumen of the tract. The lumen contained granular, amorphous fibrinous debris and leukocytes. Through this central zone, and in the adja-

cent portion of the granulation tissue zone, were numerous clumps of short-chain streptococci. In the more peripheral portions of the granulation tissue zone were dense collagenous fibers and fragments of atrophic cardiac muscle. The remainder of this zone was composed of fibroblasts, young connective tissue cells, fine fibrillary

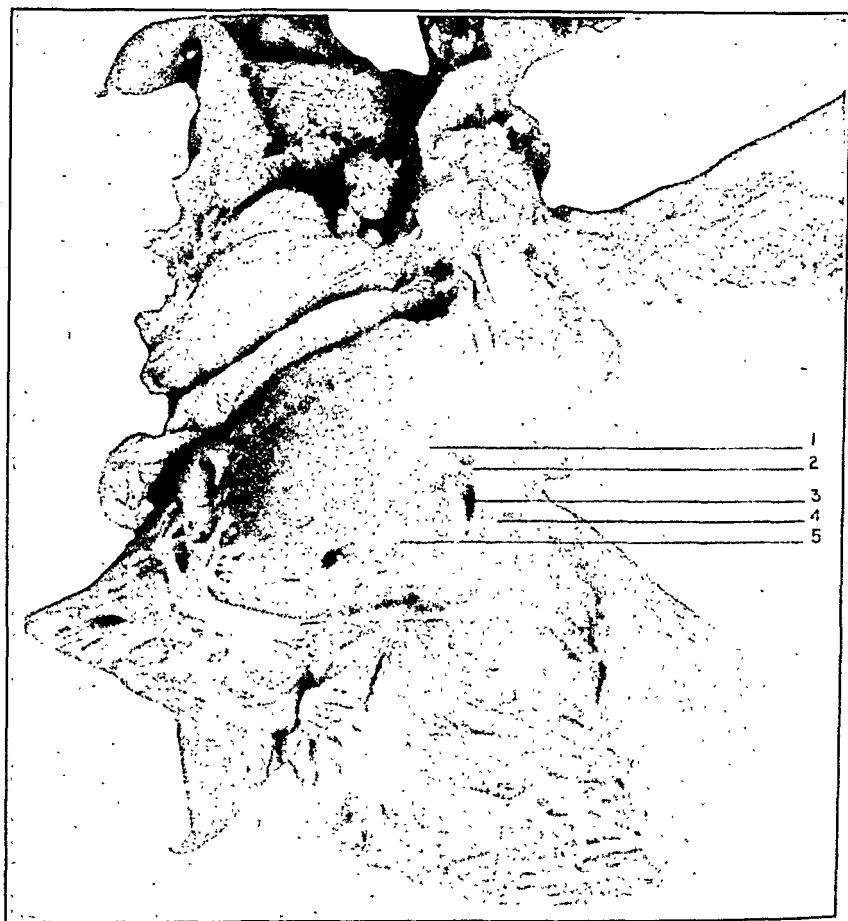


FIG. 2.—Heart opened exposing right ventricle to show ventricular opening of fistula between and below posterior pulmonary valve cusps. The intramyocardial abscess appears as a slight bulge directly below the opening of the fistula; the widened commissure is directly above it. (1) Right posterior pulmonary valve cusp; (2) right-left pulmonary commissure; (3) ventricular opening of fistula; (4) left posterior pulmonary valve cusp; (5) bulge of intracardiac abscess.

connective tissue and numerous capillaries. The entire zone was sparsely infiltrated with polymorphonuclear leukocytes, and lymphocytes, the cellular infiltration becoming denser centrally.

In the sections taken through the ventricular end, the granulation tissue zone was wider, the adult fibrous tissue greater in amount

than in those from the aortic end. In these sections, as well as in the sections through the cardiac wall abscess, the myocardium was diffusely infiltrated with polymorphonuclear leukocytes, the infiltration becoming less marked as one passed away from these areas. In sections through the aortic end, no myocardial cellular infiltration was present nor was any present in sections through various portions of the heart away from the tract.

The kidneys contained discrete abscesses. The liver and kidneys showed diffuse cloudy swelling. The splenic sinuses and pulp showed a marked acute congestion.

Discussion. Two possible modes of formation of the tract described, must be considered. Either it is congenital or the tract is the result of ulceration of the septum by the infectious process. It seems to us that the former is the more likely explanation.

Grossly and histologically, the evidence points to the fistula as one of long duration, apparently antedating the recent necrotizing process. The aortic end of the fistula is markedly thickened, and except for a very small ulcerated area, its lining is smooth. This end of the tract is covered by swollen, but otherwise intact, endothelial cells. No signs of an inflammatory process are apparent in the wall of the tract in sections through the aortic end, a finding to be expected if the fistula were the result of an inflammatory ulcerative process.

Further, the central infected and necrotic areas within the fistula are separated from the myocardial wall of the tract by a zone of organizing granulation tissue. In the more peripheral portions of this zone, adult collagenous connective tissue fibers are present. The inflammatory cellular exudate is present only in the centralmost portion of the thrombus. As the periphery of the thrombus is approached, the cellular content becomes much less marked, while the zone adjacent to the myocardial wall contains only an occasional wandering cell and no organisms. The myocardium lining the tract shows no cellular infiltration. The only point at which the myocardium is invaded is the right ventricular wall abscess, which is in direct continuity with the ventricular end of the fistulous tract. At this point the fistula is narrowest, and here the bacterial and cellular content of the contained thrombus is greatest. These findings suggest a previous fibrin deposition, sterile thrombus formation and subsequent organization of the thrombus within the fistula. This apparently preceded the acute necrotizing process which is of more recent development and without, as yet, any evidence of organization (healing).

A comparison of the degree of fibrin layering and organization in various portions of the fistula is of considerable importance. Examination of the sections showed the most organized fibrin and the greatest amount of adult collagen near the ventricular end of the tract. This point, contiguous with the myocardial abscess, showed

the greatest amount of inflammatory reaction centrally. If the fistula were purely of inflammatory origin, the smallest degree of organization of the thrombus is to be expected at this point; whereas the appearances are quite compatible if the tract antedated the acute inflammatory process.

The absence of an endothelial lining along the tract wall does not militate against the theory of a congenital origin. The tract narrowed progressively toward the ventricle, and sterile thrombus formation seems to have proceeded from this point, the probable site of greatest blood puddling, toward the aorta. In time, the entire wall was covered by thrombus, the underlying endothelium probably being destroyed in the process. That [the] process was not complete is evidenced by the presence of an endothelial lining in the

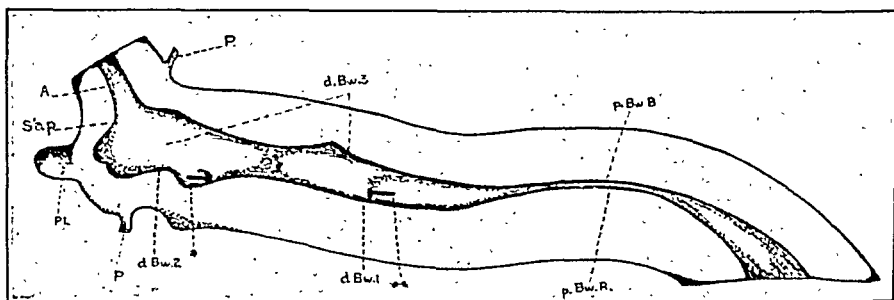


FIG. 3.—Left half of model by Julius Tandler of the bulbus cordis of the Embryo H6, divided longitudinally. A, aorta (4 aortic arch); d.Bw. 1-3, distal bulbar swelling; p, attachment of pericardium; p.Bw A-B, proximal bulbar swelling A and B; PL, pulmonary artery (6th aortic arch); S.a.p., septum aortopulmonale; *, point at which the sound in the lumen of the pulmonary artery disappears, being covered by the fusion of the distal bulbar swellings 1 and 3, forming distal bulbar septum; **, point at which the sound again appears in the common lumen. The subdivision of the common efferent tube is produced distally by the septum aortopulmonale, in the middle region by the distal bulbar septum and proximally by the proximal bulbar septum. Between these three portions of the partition there are two points of communication, in which the ends of the sounds are visible. (From Keibel and Mall, Embryology, vol. 2, Fig. 384, p. 552.)

sections through the aortic end of the tract, where thrombus was not in contiguity with the wall.

To explain the congenital defect found in this case, it will be necessary to review briefly the embryologic mechanism involved in the formation of the septum dividing the aorta and pulmonary artery.^{4,5}

Three factors take place in the subdivision of the efferent tube:

1. The proximal bulbar swellings;
2. The distal bulbar swellings;
3. Septum aortopulmonale.

The proximal bulbar swellings consist of two endocardial thickenings in the proximal portion of the bulbus (Fig. 3). Swelling A, beginning distally on the left posterior wall, passes to the left,

finally to disappear proximally on the right anterior bulbar wall. Swelling B begins distally on the anterior wall and passes thence over the right wall to disappear proximally on the posterior bulbar wall, on the same level as Swelling A, at the junction of the bulbus and the ventricle. At a later stage A and B fuse to form the proximal septum.

A series of swellings are now developed in the distal half of the bulb but they do not present the regularity of form and occurrence that obtains in birds and reptiles. These distal swellings are 4 in number. Starting with the right distal one and proceeding to the left and backward they are denoted by the numbers 1 to 4. When followed proximally, they are seen to run downward on the bulbar wall in a clockwise spiral. Swellings 1 and 3 are strongly developed while 2 and 4 are weaker. Swelling 1 lies distally on the right wall of the bulbus and passes gradually backward and to the left, joining Swelling A at a later stage. Swelling 3 begins above on the left wall and passes to the right anterior one as it descends, later joining Swelling B. Eventually, 1 and 3 fuse to form the distal septum. Swellings 2 and 4 have a position between Swellings 1 and 3, Swelling 2 passing from above and behind downward into the left, and Swelling 4 from above and in front, downward to the right.

The septum aortopulmonale arises as a partition between the sixth and fourth pairs of aortic arches, grows proximally and extends into the efferent tube, dividing it distally into aorta and pulmonary artery.

At this stage the three portions making up the septum are still distinctly separated. The aorta and pulmonary artery are still in communication at three points, viz.:

1. Between the aortopulmonale septum and the distal end of the distal bulbar swellings.

2. Between the proximal end of the distal bulbar swelling and the distal end of the proximal bulbar Swellings A and B, and

3. Proximal to the proximal bulbar Swellings A and B.

Normally, after the formation of the septum, the aortic side contains one-half of each Swelling 1 and 3 and all of Swelling 4, and the pulmonic side the other halves of Swellings 1 and 3, and all of Swelling 2. The most proximal portions of these swellings hollow out on their distal slopes, forming the anlage of the semilunar valves.

We can explain our defect in one of two ways:

1. The proximal and distal septa fuse and the aortic valves form from their half of the proximal portions of the distal bulbar swellings. The communication between the distal bulbar septum and the septum aortopulmonale remains patent and the pulmonic valves form from the proximal end of the septum aortopulmonale.

2. Or else, since the distal bulbar swellings are often irregular as to form and occurrence, we can conceive of a persistent communication in the distal bulbar septum itself, immediately distal to the

aortic valves, and the pulmonic valves arising immediately distal to such a defect.

Of great importance in connection with a congenital origin of the tract is the relative position of the aortic and pulmonic valve cusps in this case. Measured from the anterior end of the apex at a point exactly midway between the left and right surfaces of the interventricular septum, these valves rose at points 5.9 cm. and 6.7 cm. respectively, a difference of 0.8 cm. Similar measurements of 20 hearts from children of the same age, in whom no cardiac or aortic anomalies or pathologic changes were present disclosed a difference of not more than 0.2 cm., with the variation of distance greater for the aortic valve in 12 instances and for the pulmonary valve in 8 instances. The difference noted in this case suggests that the direction of the fistula was influenced by an abnormally high origin of the pulmonary valve cusps, above the level of origin of the aortic cusp, both probably arising from the distal bulbar septum.

Summary. 1. A case is presented of an acute bacterial infection superimposed upon a heart containing a fistula between aorta and right ventricle and a bicuspid aortic valve and coarctation of the aorta.

2. An explanation is offered for the presence of the fistula.

Dr. Maude Abbott, to whom the evidence was submitted has concurred with this explanation. (See Nelson Loose-leaf article, 1932 continuation, p. 272).

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SERIAL NON-PROTEIN NITROGEN STUDIES AND THEIR PROGNOSTIC SIGNIFICANCE IN ACUTE CORONARY OCCLUSION.

A PRELIMINARY REPORT.*

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CORONARY occlusion, a clinical entity that was first described by Herrick in 1912,¹ has become one of the most interesting diseases that the general practitioner and internist see today. Heberden² in 1768 first described angina pectoris, a condition with which

* Submitted for publication January 26, 1933.

coronary occlusion is closely associated and often confused. Jenner³ first associated angina pectoris with diseases of the coronary arteries.†

"When you are acquainted with my motives, I presume you will pardon the liberty I take in addressing you. I am prompted to it from a knowledge of the mutual regard that subsists between you and my worthy friend Mr. Hunter. When I had the pleasure of seeing him at Bath last autumn, I thought he was affected with many symptoms of the angina pectoris. The dissections (as far as I have seen) of those who have died of it, throw but little light upon the subject. Though in the course of my practice I have seen many fall victims to this dreadful disease, yet I have only had two opportunities of an examination after death. In the first of these I found no material disease of the heart, except that the coronary artery appeared thickened.

"As no notice had been taken of such a circumstance by anybody who had written on the subject, I concluded that we must seek for other causes as productive of the disease: but about 3 weeks ago, Mr. Paytherus, a surgeon at Ross, in Herefordshire, desired me to examine with him the heart of a person who had died of angina pectoris a few days before. Here we found the same appearance of the coronary arteries as in the former case. But what I had taken to be an ossification of the vessel itself, Mr. P. discovered to be a kind of firm fleshy tube, formed within the vessel, with a considerable quantity of ossific matter dispersed irregularly through it. This tube did not appear to have any vascular connection with the coats of the artery, but seemed to lie merely in simple contact with it.

"As the heart, I believe, in every subject that has died of the angina pectoris, has been found extremely loaded with fat; and as these vessels lie quite concealed in that substance, is it possible this appearance may have been overlooked? The importance of the coronary arteries, and how much the heart must suffer from their not being able duly to perform their functions (we cannot be surprised at the painful spasms) is a subject I need not enlarge upon, therefore shall only just remark that it is possible that all the symptoms may arise from this one circumstance.

"As I frequently write to Mr. H. I have been some time in hesitation respecting the propriety of communicating the matter to him, and should be exceedingly thankful to you, Sir, for your advice upon the subject. Should it be admitted that this is the cause of the disease, I fear the medical world may seek in vain for a remedy, and I am fearful (if Mr. H. should admit this to be the cause of the disease) that it may deprive him of the hopes of a recovery."

In coronary occlusion we may find a typical history and physical findings such as we find in typical lobar pneumonia, or again it may be as confusing as any atypical pneumonia. The sequence of events—(1) pressing or crushing pain in the region of the precordium (the pain radiating down left arm or up the left side of the neck); (2) a fall in blood pressure; (3) dyspnea associated with cyanosis or ashy-gray appearance; (4) fever and leukocytosis; (5) precordial friction rub—has become well known to many.

There is, however, one point or factor which I believe needs emphasis, and that is the function of the kidney in this disease. We all know that a certain pressure is needed in the arterial system

† As this letter (written year 1778) is not easily available it is given herewith.

for the kidney to carry on its normal function. In fact we even say that in essential hypertension the elevated blood pressure is a safety mechanism so that the vital renal function may be performed, and we know that this is given as one argument for not lowering the blood pressure in these individuals. My observations in acute coronary occlusion do not coincide with this thought. As shown by Cases 15 and 16, the drop in blood pressure and a definite and marked diminution in urinary output are not sufficient in themselves to account for the non-protein nitrogen factor in acute coronary occlusion; for, although both of these cases had a decided and marked drop in blood pressure and a diminution in urinary output, the non-protein nitrogen did not become markedly elevated.

TABLE 1.—CASES 15 AND 16 ILLUSTRATING DROP IN BLOOD PRESSURE AND DIMINUTION IN URINARY OUTPUT. (NOTE NON-PROTEIN STUDIES IN TABLE 2, CASE 16.)

Case 15.	Blood pressure.	Date.	Fluid intake, cc.	Urinary output, cc.
S. S.	150/90	10-14-32	None	recorded
	105/75	10-15		"
	74/56	10-16		"
	108/70	10-17		"
	102/70	10-18	3420	1320
	90/70	10-19	1770	500
	120-80	10-25	1970	840
	118/90	11- 1	1960	1560
	130/84	11-14	1300	900
Case 16.				
C. B.	140/90	1-14-33 (9.00 A.M.)		
	110/80	1-14 (7.20 P.M.)		
	100/80	1-15	2490	500
	88/65	1-16 (Fibrillating) . . .	2950	400
	85/60	1-19 (Normal rhythm; quinidin)	1100	650
	75/55	1-20	2300	1100
	85/60	1-21	1830	880
	70/45	1-23	2150	600

My particular observation concerns the retention of non-protein nitrogen in the blood plasma in 16 cases of coronary occlusion (Table 2).

An analysis of this tabular study indicates that 9 out of the 16 cases showed a non-protein nitrogen retention that was above 40 mg. per 100 cc. (1 had 40 mg.). Of the 6 fatal cases in this group, only 1 showed a non-protein nitrogen below 40. The 3 cases that showed progression or retention of waste products in the blood stream or continued elevation without necessarily progression in amount of non-protein nitrogen terminated fatally. Three individuals in whom serial non-protein nitrogen studies were made and who showed a definite tendency toward lowering of the non-protein nitrogen value recovered. None of the autopsied cases showed evidence of any marked nephritis.

Summary. 1. Sixteen cases of coronary occlusion are presented with special reference to the retention of non-protein nitrogen as a prognostic factor.

TABLE 2.—TABULAR STUDY OF 16 CASES OF CORONARY OCCLUSION.

Name.	Age.	Dates of attack.	Non-protein nitrogen (mg. per 100 cc.).	Kidney function test.	Urine.
1. J. B.	64	Day of admission, 3/24/32	48—3/28/32	None	3/25/32: sp. gr. 1820; f. tr. alb.
2. S. A.	68	July, 1930	46—1/22/31 (Creatinin 3.2)	None	1/29/31; 2 plus alb.; sp. gr. 1022; no casts.
3. P. D.	49	Day of admission, 2/26/31	75—2/28/31 (Creatinin 3.5)	None	2/27/32: sp. gr. 1021.
4. S. L.	58	No history of pain; entered 1/26/31 in coma; diabetic.	30—3/16/31 32—1/26/31	None	1/26/31: 4 plus sugar; neg. acetone; diacetic plus.
5. G. H.	58	Attack, 4/11/31	37—4/17/31	None	4/17/31: sp. gr. 1020; ft. tr. alb.
6. C. P.	58	Attack, June 1931; too numerous to count after admission 8/1/31	71—8/ 3/31 95—8/ 7/31 133—8/10/31 185—8/11/31 215—8/14/31 30—8/17/31	None	8/3/31: sp. gr. 1026; alb. plus; 8/7/31: sp. gr. 1021; tr. 5 to 6 casts; 8/14/31: sp. gr. 1012; alb. plus; 3 to 4 casts; few red blood cells.
7. A. G.	51	9 attacks since 1912; last attack 8/15/31, on day of admission	30—8/17/31	P.S.P. 57%; 9/4/31; Mosenthal negative 9/6/31	Neg.
8. M. McM.	66	First attack 9/4/31; 3 attacks, last 9/9/31, 9/10/31; admitted 9/9/31	33—9/10/31	None	9/10/31: sp. gr. 1022; plus alb.; occas. R.B.C.; no casts; 9/20/31; sp. gr. 1018; alb. neg.
9. J. T.	56	Attack Sept. 1931; admitted 11/23/31	42—11/24/31	None	11/24/31: sp. gr. 1026; sugar pos.; 12/5/31: sp. gr. 1010; neg.; 12/26/31: ft. tr. alb.; sp. gr. 1012; neg.
10. H. DeW.	60	July 1931 and 11/21/31; admitted 11/26/31	110—11/27/31 42—11/30/31 38—12/ 4/31 34—12/10/31	None	11/27/31: sp. gr. 1025; ft. tr. alb.; 11/29/31: sp. gr. 1029; neg.
11. A. P.	42	Oct. 1931; admitted 12/9/31	34—12/10/31	P.S.P. 34%, 2 hrs. intraven.; Mosenthal fixed high gravity, 12/14/31	12/10/31: sp. gr. 1025; tr. alb.; 12/11/31: neg.; sp. gr. 1020.
12. B. W.	49	Mar. 1930; 3 attacks since; last attack 3/5/32; admitted 3/6/32	41—3/ 6/32 40—3/ 9/32 142—3/28/32	None	3/4/32: neg.; sp. gr. 1031; 3/18/32: neg.; 3/26/32: neg.
13. A. M. B.	65	Nov. 1931 to April 24, 1932; 5 attacks	60—4/30/32 47—5/ 3/32 40—5/10/32 54—6/10/32 40—8/9/32	P.S.P. 10%, 2 hrs.	4/30/32: neg.; 5/17/32: neg.
14. L. M.	55	March 1932	40—8/9/32	None	8/10/32: neg.; sp. gr. 1010.
15. S. S.	48	Early part of Sept. 1932, first attack; sev'r'l attacks since; worst 11/21/32	29—10/18/32 45—11/ 5/32 27—11/14/32	P.S.P. 85%, 10/18/32, 2 hrs. intrav.	Neg. on 3 occasions.
16. C. B.	58	Day of admission 1/14/33	39—1/16/33 35—1/20/33 34—1/23/33	P.S.P. 65%, 1/23/33	Neg. except 1 plus alb., 1/23/33.

TABLE 3.—ELECTROCARDIOGRAMS OF CASES OF ACUTE CORONARY OCCLUSION.

Electrocardiograms.		Outcome.
1. J. B.	3/25/32.	No death.
A. Auricular fibrillation.		
B. Left ventricular preponderance.		
C. Freq. ventricular premature contractions.		
D. Slurring and notching of <i>Q-R-S</i> complexes in Leads II and III.		
2. S. A.	1/29/31.	Autopsy proved.
A. Low voltage, all 3 leads.		
B. Slurred <i>Q-R-S</i> complexes, all 3 leads.		
C. Ill-defined <i>T</i> waves in all 3 leads.		
3. P. D.	2/6/31.	No death.
A. Auricular fibrillation.		
B. Slurred <i>Q-R-S</i> complexes in all 3 leads.		
C. Notched <i>Q-R-S</i> complexes in Lead III.		
D. Diphasic <i>T</i> waves in Leads I and II; inverted <i>T</i> waves in Lead III.		
4. S. L.	None.	Autopsy 1/27/31; coronary occlusion.

TABLE 3.—Continued.
Electrocardiograms.

	Outcome.
5. G. H. 4/22/31. A. Slurred <i>Q-R-S</i> complexes in all 3 leads. B. Left ventricular preponderance. C. High take-off of the <i>T</i> waves in Leads I and II.	No death.
6. C. P. 8/8/31. A. Slurred and notched <i>Q-R-S</i> complexes in all 3 leads. B. Deep <i>Q</i> wave in Lead III.	Autopsy 8/15/31; coronary occlusion; few small anemic infarcts in kidneys.
7. A. G. 8/26/31. A. Slight sinus arrhythmia. B. Neg. <i>T</i> waves in Leads II and III, with high <i>T</i> wave take-off.	No death; diag. chronic nephritis March, 1929; Brooklyn Navy Hosp.; gross anasarca, ++ alb.; urine, occasional R.B.C.; no casts; no blood chemistry done. Mosenthal, negative.
8. M. McM. 9/10/31. A. Sinus tachycardia; neg. <i>T</i> waves in Lead I; high take-off of <i>T</i> wave in Lead I. B. Left ventricular preponderance.	No death.
9. J. T. 11/28/31. A. Sinus tachycardia; iso-electric or neg. <i>T</i> waves in all 3 leads.	No death.
10. H. DeW. 11/28/31. A. Sinus tachycardia; slight sinus arrhythmia; left ventricular preponderance. B. Slurred or notched <i>Q-R-S</i> complexes in all 3 leads; iso-electric or diphasic <i>T</i> waves in all 3 leads.	No death.
11. A. P. 12/14/31. A. Slight sinus arrhythmia. B. Marked left ventricular preponderance. C. Notched <i>Q-R-S</i> complexes in Leads I and III. D. Neg. <i>T</i> waves in Lead I.	No death.
12. B. W. 3/7/32. A. Low voltage slurred <i>Q-R-S</i> complexes in Leads I and III; poorly defined <i>T</i> waves in all 3 leads; freq. ventricular premature contraction. 3/15/32. A. Low voltage complexes; right ventricular preponderance. B. Sinus tachycardia; slight sinus arrhythmia.	Autopsy, 4/1/32; coronary occlusion; kidneys neg. except mild arteriosclerosis.
13. A. M. G. 5/7/32. A. Left ventricular preponderance; freq. ventricular premature contractions. B. Low voltage, slurring and notching of <i>Q-R-S</i> complexes in all 3 leads.	Discharged; edema, etc., increasing.
14. L. M. None.	Died, 8/14/32; autopsy, coronary occlusion.
15. S. S. 10/17/32. A. Slurred <i>Q-R-S</i> complexes in all 3 leads. B. Inverted <i>T</i> waves, Leads II and III. C. Deep <i>Q-III</i> . 10/22/32. A. Sinus tachycardia. B. Slight sinus arrhythmia. C. Slurred <i>Q-R-S</i> complexes in all 3 leads; inverted <i>T</i> wave in Leads II and III. D. Deep <i>Q-III</i> .	Recovery.
16. C. B. 1/17/33. Slurred and notched <i>Q-R-S</i> complexes, Lead I; poorly defined <i>T</i> waves, Lead I; diphasic <i>T</i> waves, Lead II.	Good, 1/21/33—day of writing.

TABLE 4.—FATAL CASES SHOWING PROGRESSION OR CONTINUED EVALUATION OF NON-PROTEIN NITROGEN.

Name.	Age.	Dates of attack.	Admission.	Non-protein N (mg. per 100 cc.).
C. P.	58	June, 1931; then too numerous to count	8/1/31	71—8/ 3/31 95—8/ 7 133—8/10 185—8/11 215—8/14
B. W.	49	March, 1930; 3 attacks since 3/5/32	3/6/32	41—3/ 7/32 40—3/ 9 142—3/28
A. M. B.	65	November, 1931 to April, 1932, 5 attacks		60—4/30/32 47—5/ 3 40—5/10 54—6/10

TABLE 5.—RECOVERED CASES SHOWING RETROGRESSION OF NON-PROTEIN NITROGEN.

Name.	Age.	Dates of attack.	Admission.	Non-protein N (mg. per 100 cc.).
P. D.	49	2/26/31	75— 2/28/31 (Creat., 3.5) 30— 3/16
H. DeW.	60	July and November, 1931	11/26/31	110—11/27/31 42—11/30 38—12/ 4
S. S.	48	Early part of September, 1932 first attack; several attacks since; worst 11/21/32		29—10/18/32 45—11/ 5 27—11/14

TABLE 6.—GROUP SHOWING ELEVATED NON-PROTEIN NITROGEN STUDIES IN ACUTE CORONARY OCCLUSION.

Name.	Age.	Dates of attack.	Admission.	Non-protein N (mg. per 100 cc.).
P. D.	49	2/26/31	75— 2/28/31 (Creat., 3.5) 30— 3/16
H. DeW.	60	July and November, 1931	11/26/31	110—11/27/31 42—11/30 38—12/ 4
C. P.	58	June, 1931; then too numerous to count after admission	8/1/31	71— 8/ 3/31 95— 8/ 7 133— 8/10 185— 8/11 215— 8/14
B. W.	49	March, 1930; 3 attacks since last attack, 3/5/32	3/6/32	41— 3/ 7/32 40— 3/ 9 142— 3/28
A. M. B.	65	November, 1931 to April 24, 1932, 5 attacks		60— 4/30/32 47— 5/ 3 40— 5/10 54— 6/10
J. B.	64	3/24/32	48— 3/28/32
S. A.	68	July, 1930		46— 1/22/31 (Creat., 3.2)
J. T.	56	September, 1931	11/23/31	42—11/24/32
S. S.	48	Early September, 1932 first attack; several since; worst 11/21/32		29—10/18/32 45—11/ 5 27—11/14

2. From this small group of cases it seems as if (a) a rising non-protein nitrogen or (b) a non-protein nitrogen that remains elevated in the blood plasma is of ill omen.

3. More attention should be paid to blood chemistry studies during coronary occlusion as a prognostic aid.

4. A lowering of the blood pressure and a diminution in urine output will not alone explain the rise in non-protein nitrogen in acute coronary occlusion.

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SERUM CALCIUM IN NORMAL BOYS.

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SERUM calcium studies were made on 511 cases whose ages ranged from 8 to 20 years. It is within this age group that a paucity of information exists in the current literature.

Cantarow,¹ in his monograph on calcium metabolism, regards the normal range for all ages to be from 9.2 to 11 mg. per 100 cc. of blood. Katzenelbogen and Goldsmith,² in a more recent review of the literature, place the extreme normal limits for all ages between 8.6 and 12 mg. per cent. A few studies have been made exclusively on children. Mayer³ found, among children age between 4 and 10 years, the serum calcium to average 11.38 mg. per cent. Greisheimer⁴ *et al.* studied 22 boys between the ages of 7 to 17 years and found that their serum calcium ranged from 10 to 13.5 mg. per cent, with an average of 11.6 mg. per cent. Sokolovitch,⁵ in 5 normal children, reported their calcium to be between 9.72 and 11.4 mg. per cent.

Our study was made during the last 2 weeks of July and the first 2 weeks of August, 1932. During this period more than 1 quart of milk was given each boy daily. Fresh fruits and vegetables were abundant, and a well-balanced mixed diet was given. The blood was obtained by venoclysis before breakfast in every instance.

The method used to determine the amount of serum calcium present was that of Clark and Collip.⁶ Table 1 gives the distribution of cases. The serum calcium findings of our subjects ranged from 7.6 to 12.5 mg. per cent.

TABLE 1.—TOTAL DISTRIBUTION.

No. of boys.	Calcium, mg., per cent.	Graphic distribution.
1	7.6	—
0	7.7	
1	7.8	—
3	7.9	—
4	8.0	—
2	8.1	—
5	8.2	—
5	8.3	—
4	8.4	—
8	8.5	—
4	8.6	—
8	8.7	—
9	8.8	—
11	8.9	—
15	9.0	—
25	9.1	—
25	9.2	—
26	9.3	—
28	9.4	—
30	9.5	—
30	9.6	—
32	9.7	—
35	9.8	—
27	9.9	—
25	10.0	—
17	10.1	—
21	10.2	—
28	10.3	—
15	10.4	—
20	10.5	—
12	10.6	—
5	10.7	—
5	10.8	—
3	10.9	—
5	11.0	—
2	11.1	—
4	11.2	—
3	11.3	—
4	11.4	—
0	11.5	
1	11.6	—
0	11.7	
1	11.8	—
0	11.9	
1	12.0	—
0	12.1	
0	12.2	
0	12.3	
0	12.4	
1	12.5	—

Disregarding the highest and lowest 5 per cent of our distributions, we find our normal limits are from approximately 8.5 to 10.8 mg.

per cent. Considering 8.6 to 12 mg. per cent as the extreme normal limits it is seen from the table that 33 are below 8.6 mg. and only 1 above 12 mg.

Greisheimer⁴ *et al.* found that the serum calcium content definitely decreased with age. Their average for boys at 12 years of

TABLE 2.—DISTRIBUTION ACCORDING TO AGE.

Calcium, mg., per cent.	Age.																			Total.
	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.	18.	19.	20.							
7.6	1	1
7.7
7.8	1	1
7.9	1	1	1	3
8.0	3	1	4
8.1	1	1	..	1	3
8.2	1	1	3	5
8.3	2	2	1	5
8.4	1	1	..	1	1	1	..	1	..	1	5
8.5	2	2	1	1	1	7
8.6	1	1	1	1	4
8.7	2	1	..	1	2	2	8
8.8	1	1	..	2	3	1	1	1	1	9
8.9	1	..	1	2	..	1	4	1	10
9.0	1	1	1	5	1	6	15
9.1	1	..	2	3	3	5	7	3	24
9.2	2	4	5	3	5	4	2	2	27
9.3	1	..	1	4	2	4	9	4	25
9.4	2	2	3	6	8	4	3	2	30
9.5	1	..	3	3	2	8	9	3	29
9.6	1	3	3	4	7	9	2	1	30
9.7	1	2	4	6	10	8	3	34
9.8	4	5	11	9	9	3	32
9.9	2	1	1	6	4	9	4	27
10.0	2	..	3	4	11	2	1	..	1	24
10.1	1	5	3	2	1	5	1	18
10.2	.	1	3	2	9	5	1	21
10.3	2	4	5	7	9	1	28
10.4	3	..	4	6	1	1	15
10.5	2	3	6	2	7	20
10.6	1	1	2	2	4	2	12
10.7	1	..	1	2	..	1	5
10.8	1	..	1	1	2	5
10.9	1	2	3
11.0	1	3	1	5
11.1	1	1	2
11.2	1	..	2	1	4
11.3	1	1	2
11.4	1	1	2	1	5
11.5
11.6	1	1
11.7
11.8	1	1
11.9
12.0	1	1
12.1
12.2
12.3
12.4
12.5	1	1
Total	.	1	2	9	17	32	66	80	125	126	43	6	3	1	511

TABLE 3.—DISTRIBUTION ACCORDING TO NATIONALITIES.

Calcium, mg., per cent.	American.	Polish.	Italian.	Negro.	Others.
7.6	1		
7.7					
7.8	1
7.9	1	1	..	1
8.0	2	1	1		
8.1	2		
8.2	2	2	..	1	
8.3	2	1	1	1
8.4	1	..	1	2	
8.5	2	2	4	
8.6	1	3	
8.7	1	..	2	4	1
8.8	3	..	1	2	3
8.9	3	4	3
9.0	2	2	3	5	3
9.1	3	3	8	5	6
9.2	5	2	4.	12.	2.
9.3	3	5.	6	8	4
9.4	7.	3	5	9	5
9.5	9	4	7	6	4
9.6	7	6	8.	6	3
9.7	9.	5	5	11.	4.
9.8	5	5.	8	8	7
9.9	9	3	2	11	2
10.0	4	7	4	7	2
10.1	6	2	2	6.	2
10.2	2.	4.	5.	5	5.
10.3	5	4	6	7	6
10.4	5	..	7	..	3
10.5	4	3	5	8	
10.6	4	1	1	5	1
10.7	1	1	3
10.8	1	1	..	2	1
10.9	1	1	1
11.0	2	2	1		
11.1	1	1
11.2	2	1	..	1
11.3	1	1	..	1	
11.4	1	1	..	2	
11.5					
11.6	1
11.7					
11.8	1			
11.9					
12.0	1			
12.1					
12.2					
12.3					
12.4					
12.5	1			
Total	108	79	101	146	77

Others:

Slavish	6	Austrian	4	Hungarian	18
Irish	8	Jewish	6	Ukrainian	2
German	9	Russian	16	Lithuanian	8

age was 11.6 mg., while men at 79 years of age was 10 mg. In our study we found the following for each age group:

- 11 years of age: average, 9.5 mg. per cent; average deviation, ± 0.6 .
- 12 years of age: average, 9.6 mg. per cent; average deviation, ± 0.4 .
- 13 years of age: average, 9.5 mg. per cent; average deviation, ± 0.58 .
- 14 years of age: average, 9.5 mg. per cent; average deviation, ± 0.43 .
- 15 years of age: average, 9.7 mg. per cent; average deviation, ± 0.57 .
- 16 years of age: average, 9.7 mg. per cent; average deviation, ± 0.73 .
- 17 years of age: average, 9.6 mg. per cent; average deviation, ± 0.5 .

Apparently there is no decrease in serum calcium in these age areas. It may be that the decrease begins at a later period in life. Howland and Marriott, Kramer, Tisdall and Howland, and Anderson as quoted by Cantarow¹ found no essential difference between the serum concentration in children and adults.

Table 2 gives a composite of the calcium findings according to age. With the thought that there may be some differences, influenced by nationality or race, Table 3 was compiled. No influences, by nationalities or races, were discerned as seen by the central tendencies of the various groups shown below.

The average calcium milligram per cent for the 5 racial categories is as follows:

- American, 9.7; average deviation, ± 0.5 .
- Polish, 9.8; average deviation, ± 0.6 .
- Italian, 9.5; average deviation, ± 0.5 .
- Negro, 9.6; average deviation, ± 0.5 .
- Others, 9.7; average deviation, ± 0.5 .

To discover any possible relationships between behavior, mental development and calcium metabolism, certain psychologic data were obtained. These included the general mental level of each boy of the study, a list of those who have spent 2 or more periods in the special discipline cottage and a list of those who were quartered in the special group of unusually unstable and inadequate boys. No relation was found and the details of this part of the study will be published in a separate paper. As these boys were also all in apparently good physical condition, we feel that they may be regarded as normal.

Conclusions. The serum calcium findings on 511 normal boys, between the ages of 8 and 20 years, range from 7.6 to 12.5 mg. per cent. Of the total number reported, 33 were found below and 1 above the extreme normal limits of 8.6 and 12 mg. per cent. Disregarding the highest and lowest 5 per cent of our distribution, we find our normal limits are from approximately 8.5 to 10.8 mg. per cent. No progressive decrease was found with age in our group. Nationality and race, in our findings, showed no influence on serum calcium metabolism.

NOTE.—We desire to thank Dr. John Reinhold of the Philadelphia General Hospital for his help in furnishing the standard oxalate solution and in useful suggestions and criticisms.

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CALCIUM PRECIPITATIONS AND ALKALINIZATION IN AËROBIC TISSUE CULTURES.

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IN a recent paper Demuth¹ described the occurrence of dense, grayish white precipitation rings, which appeared dirty brown in transmitted light, surrounding the explant in the tissue culture medium. Demuth believes that their formation depends upon the glycolytic activity of the cells and concludes from his investigations that these rings are mainly composed of calcium lactate and are formed according to the principle active in the production of Liesegang rings. He obtained these rings quite regularly when small amounts of calcium chlorid were added to the medium, and especially in cultures of malignant cells thus treated. But he observed them also occasionally in well-growing cultures of untreated normal tissues, which, as he remarked, do not produce any excessive amounts of lactic acid, indicating that other slightly soluble salts might form or participate in the formation of precipitates in tissue cultures.

During an investigation by the authors of the effects of various amino-acids upon the differentiation and proliferation of cells *in vitro*, similar formations were first observed in a series of Carrel flask cultures which had been explanted in an ordinary chicken plasma-embryo extract medium to which small amounts of arginine had been added. A more thorough study of the nature and causative mechanism of these precipitations seemed to be indicated, as our findings differed in certain respects from those made by Demuth, and as this author's explanations in regard to the causes and composition of these rings did not appear to be quite applicable to the precipitations observed in our cultures.

The precipitations appearing in our cultures were of grayish-white color and were of three different types. In some of the cultures a delicate, veil-like, white opaque membrane was formed which covered the whole surface of the medium and was loosely attached to it. The growth of the explanted cells was apparently not interfered with. In other cultures the clear plasma medium changed around the explant into a milky white material which gradually extended diffusely into the peripheral parts of the medium, leaving only a narrow, clear zone around the explant. The cellular proliferation in cultures with this type of precipitation was in general very scanty or entirely absent, indicating that the physico-chemical changes brought about by the precipitations, or causing them, were unfavorable to growth. The third variety of precipitations observed was similar to the type described by Demuth. While ring formation was seen in some instances in cultures with scanty cell growth, the great majority of the precipitation rings appeared in cultures which showed a good and healthy cell growth (Figs. 1 and 2). It may be mentioned that the above described precipitations were more frequently found in cultures of normal embryonic chicken cells (chondrioblasts, heart fibroblasts) than in cultures of malignant cells (spontaneous mammary carcinoma of white mice, Walker rat sarcoma).

In agreement with Demuth's observations an irregularity in the shape and extent of these rings was sometimes noticed. There were variations in the density and width of the precipitation zone in different sectors of the rings. In other instances, the ring was primarily incomplete and surrounded the explant as a curved sausage-like formation which later on closed—a development which can be reconstructed from the ring in Fig. 1, in which the sector of the ring, secondarily filled in, can easily be recognized because it is less dense. In a few cultures an irregularly shaped precipitation wall, encircling only a part of the proliferation zone, was seen (Fig. 2). There was no appreciable difference between the sharpness of the inner and outer contours of the rings, as was noted by Demuth in his rings. It is also quite evident from the pictures that the rings sometimes interfered definitely with the proliferation and emigration of the cells, especially in cases where they penetrated the rings. There was not infrequently a crowding of cells in the zone inside the ring (Figs. 2 and 3) with evidence of disturbed nutrition of these cells, as manifested by droplet formation and decrease in cell size. Also progressive degeneration of the cells in the inner zone was not uncommon, resulting in complete destruction of these cells, leaving only a small rim of unhealthy looking cells in and beyond the region of the precipitation zone. Further evidence in regard to the damaging effect of the precipitation upon the cells was furnished by the occasional observation of incrustated cells and fibrils in the precipitation zone (Fig. 4).

The precipitations which represent an amorphous whitish material showed in the fixed and stained cultures a high affinity for hematoxylin, suggesting thereby the presence of a calcium compound. The calcium character of the precipitations was definitely established by the incineration method. After incineration of the cultures and removal of the soluble mineral salts by washing the ashed material with distilled water, delicate, concentric lamellæ of calcium oxid and phosphate remained where the precipitation rings had been located. The concentric lamellated arrangement of the calcium ash also furnished, incidentally, supporting evidence for the conception held by Demuth concerning the Liesegang ring nature of this type of precipitation.

In regard to the chemical nature of the calcium compound, Demuth has, as already mentioned, maintained that the rings consist mainly of calcium lactate, as he found that after washing the cultures repeatedly with water for several days (to remove the soluble mineral constituents from the culture) the analysis of the material containing the undissolved rings gave a calcium-lactic acid ratio approximating that present in calcium lactate. It appears doubtful, however, whether from such an analysis these conclusions can justly be drawn, as calcium lactate is moderately soluble in water and one would therefore expect that the washings with distilled water should also have resulted in the solution and removal of the precipitated calcium lactate. Demuth's lactic acid figures obtained in these explants are, moreover, the lowest mentioned in the group of cultures examined, an observation which cannot well be reconciled with his conception, as the binding of the lactic acid by the calcium should result rather in an increased accumulation of lactic acid around the explant, producing high lactic acid figures. Our own findings also do not support his contention. The addition of alcohol to the cultures does not cause a disappearance or diminution of the rings, as it should if the precipitate consisted of calcium lactate, a substance slightly soluble in alcohol, whereas calcium carbonate and calcium phosphate are almost insoluble in this medium. Acetic acid, on the other hand, added to the culture produces a rather rapid disappearance of the precipitates with moderate production of gas, indicating that at least to some extent the precipitates are composed of calcium carbonate. It is, therefore, not justifiable to assume that the precipitates represent mainly and simply calcium lactate, and Demuth's statement that the process of calcium precipitation in tissue cultures is of a complex nature, and that other factors beside the lactic acid formation by the cells contribute to and participate in all probability in their production, appears to be quite proper.

If the conditions present in tissue cultures are studied in regard to the factors which possibly may play a rôle in the precipitation of calcium salts, the following conclusions may be reached. As explants

in Carrel flasks are practically grown under more or less anaërobic conditions (Demuth), favoring the production of lactic acid, especially in malignant cell cultures, and interfering with escape of carbon dioxid, the resulting increase in acid reaction does not facilitate the precipitation of calcium salts. The possibility that the expulsion of carbon dioxid from the medium by the lactic acid may play a rôle in the formation of the precipitates, as suggested by Demuth, cannot be of major importance because of the fact that there will be established an equilibrium of the carbon dioxid content between the gaseous content of the flask and the solid and liquid medium. Moreover, the less soluble calcium salts, such as calcium carbonate and calcium phosphate, will be precipitated before the more soluble ones such as calcium lactate, in case the reaction conditions become unfavorable for the solubility of calcium salts.

That changes in the protein content of the medium surrounding the explants, caused by the utilization of these substances by the cells or their degradation by the proteases present, may play a part in the induction of the calcium precipitations observed, deserves proper attention. According to Wells, Lichtwitz has pointed out "that the precipitation of colloids results in a decrease of the amount of crystalloids which can be held in solution, wherefore the least soluble salts, those of calcium, are precipitated; by laws of osmotic pressure more calcium in solution will then enter to establish equilibrium, be precipitated, and make way for more calcium until the amount of deposit prevents further osmotic diffusion. This should lead to a calcium shell formation in the outermost zone of the affected area, which would limit the deposition." It is obvious that such a mechanism may have contributed in the formation of the calcium rings, but cannot explain the other two types of precipitations described. Supporting such a conception are the findings of Naeslund,⁴ who observed the existence of a parallelism between the proteolytic activity of actinomyces and the appearance of calcium precipitations in the medium.

To a certain extent related to the changes in the protein content of the medium is a third factor, namely, the production of substances having a special affinity for calcium salts. The decomposition of nucleoproteins and lecithin may furnish phosphoric acid which has a great tendency to form calcium phosphates. Deuteroalbumoses resulting from protein degradation have, according to Croftan,⁵ a high affinity for calcium.

In view of the fact that calcifications occur in those organs which secrete acids and become more alkaline themselves, and considering that an increase in alkalinity of tissue fluids makes calcium salts decidedly less soluble, determinations of pH of the supernatant fluid of our tissue cultures showing calcium precipitations were made and it was found that it was highly alkaline, usually varying between pH 8.2 and pH 9.0. It is evident that this finding may

account, at least to some extent, for the appearance of calcium precipitations in our cultures. But, as it stands in direct contrast to observations of other authors (Demuth,¹ and others), who reported an increasing acidity in tissue cultures, grown in Carrel flasks, an attempt was made to find the cause of this discrepancy.

In these experiments, the common Carrel flasks which were closed by a loosely fitting rubber cap containing a small cotton plug to insure better the sterility of the cultures were used. It appears that our cultures were therefore grown under aerobic conditions, while the cultures of the other investigators, who used tightly fitting caps were kept under more or less anaerobic conditions (Demuth). It could be shown that the aerobicity of the cultural conditions has a definite and constant effect upon the pH of the supernatant fluid, regardless of whether normal or malignant cells were used. The relative anaerobicity is apparently also the reason for the absence of calcium precipitations in cultures grown in sealed depression slides.

The following experiments may best demonstrate the relations existing in this respect.

Experiment I.

Chick chondrioblasts, 3 passages old, were explanted in a medium consisting of chicken plasma and embryo extract diluted 1 to 25 with Tyrode solution. Three sets of 8 cultures each were made. In 1 set the reaction of the medium was adjusted with HCl to pH 7.4, in the second set to pH 7.8 and in the third one to pH 8.2. The original pH of the Tyrode solution used was pH 7.9. The following changes in the reaction of the supernatant fluid were observed, when the caps were loosely fitted to the neck of the flasks allowing a rather free access of air:

Set original pH of medium.	pH of supernatant fluid after 24 hours.	pH of supernatant fluid after 48 hours.
pH 8.2 set	9.0	9.0
pH 7.8 set	9.0	9.0
pH 7.4 set	8.9-9.0	8.6-8.9

Experiment II.

Original pH of medium.	pH of supernatant fluid.			
	After 24 hrs.	48 hrs.	72 hrs.	96 hrs.
8.1	9.0	9.0	9.0	8.9
7.7	9.0	9.0	9.0	8.8
7.2	8.9	8.6-8.9	8.6-8.7	8.4-8.7

The flasks of the first 2 sets (pH 8.1 and 7.7) were then sealed by covering the caps and the necks of the flasks with paraffin and the pH dropped on the following day to pH 7.8 and 7.6 respectively. These results demonstrate quite definitely that aerobiosis has an alkalinizing action upon the culture medium, while anaerobiosis has an acidifying effect. It may be mentioned that the cultures were washed every second day with a properly adjusted Tyrode solution and received then an embryo extract dilution of the corresponding pH. The reaction of the supernatant fluid was determined before washing.

Similar results were obtained with cultures of heart fibroblasts. The formation of rings occurred in some instances, while the explanted muscle continued to contract.

In subsequent experiments with malignant tissues the existence of very similar relations between aërobiosis and anaërobiosis respectively and pH of the supernatant fluid was established.

Experiment III.

Small pieces of a spontaneous, white mouse mammary carcinoma were explanted in the above mentioned chicken plasma-embryo extract medium and the flasks closed in three different ways. After 24 hours' growth, the pH of the supernatant fluid was determined and the following observations were made, substantiating those reported for normal tissues:

1. Flasks closed as usually with a loosely fitting rubber cap: pH 8.7.
2. Flasks closed with a cotton plug: pH 8.7 to 8.9.
3. Flasks closed with a rubber cap and sealed with paraffin: pH below 7.2.

Experiment IV. Walker rat sarcoma.

Original pH of medium, S.O.	After 2 days.	4 days.	6 days.	8 days.	11 days.
Sealed (pH)	7.9-8.0	7.5-7.9	7.7-7.8	7.7-7.9	7.3-7.7
Unsealed (pH)	8.8	8.4-8.9	8.4-8.8	7.9-8.3*	8.7-9.0

* During the 6 to 8 day period the flasks were accidentally closed with new, tightly fitting rubber caps, which accounts for the drop in pH present in the supernatant fluid on the 8th day. The use of the old, loosely fitting caps, by which the original aërobic conditions were reëstablished, resulted promptly in a return of the alkaline reaction.

Corresponding to the above described observation on non-sealed flasks, small defects in the sealing of anaërobic cultures manifested themselves readily by their effect upon the pH of the supernatant fluid which did not become more acid, as it ordinarily does, but remained either unchanged or became even more alkaline. This is a highly sensitive reaction. The method of Hastings and Sendroy was used for the determination of the pH of the supernatant fluid in the cultures.

It may finally be mentioned that the addition of arginin or cystein to the medium had no appreciable effect upon the reaction changes observed. It was, however, noticed that precipitations occurred quite frequently in cultures to which arginin had been added. But it appears to be doubtful, if the basic character of this amino-acid has any relation to the causative mechanism.

Through the addition of various indicator dyes (cresol red, bromthymol blue) it was shown that the plasma medium has approximately the same pH as the supernatant fluid, while the explant itself and its proliferation zone appeared to be more acid. The supernatant fluid was removed and the cultures were briefly washed with a phosphate buffer solution of pH 7.0 before the indicator dyes were added to exclude any marked effect of the supernatant fluid upon the result of the test.

The above described findings seem to indicate that the presence of an alkaline reaction (pH 8-9) is one of the essential requirements for the occurrence of calcium precipitations in the medium of tissue cultures. This conception is furthermore strengthened by the observations of Naeslund⁴ on bacterial cultures grown under aërobic and anaërobic conditions. This author found that actinomyces

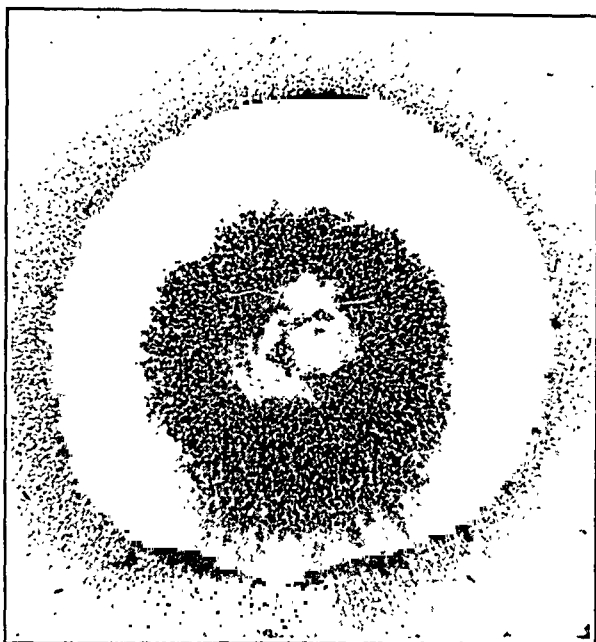


FIG. 1.—A dense and wide calcium precipitation ring which developed in the proliferation zone and which was in the beginning incomplete, becoming closed later, as evidenced by the decreased density of the precipitation in the lower sector of the ring.

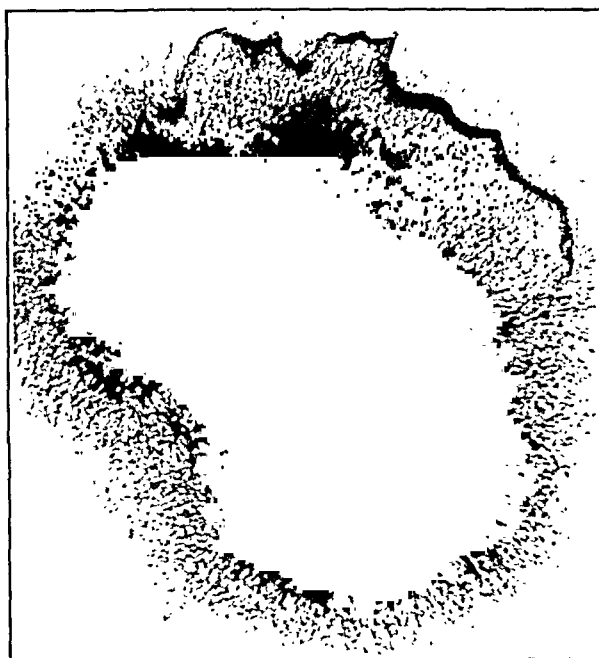


FIG. 2.—An irregular precipitation wall encircling only a part of the proliferation zone and showing the crowding of cells behind the wall.

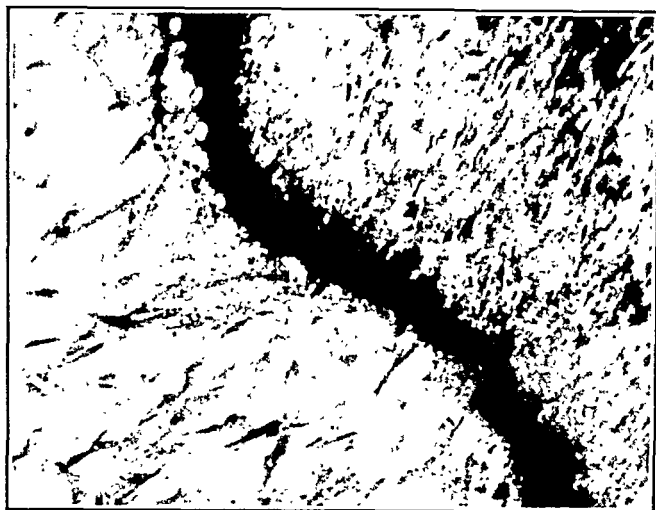


FIG. 3.—High magnification picture of the ring shown in Fig. 2, showing the cells penetrating the precipitation ring, and the difference in morphology and number between the cells located inside of the ring and those outside of the ring.



FIG. 4.—A rather weak precipitation ring with calcified cells.

grown under aërobic conditions causes an alkalization of the culture medium, the pH rising from pH 7.1 to pH 7.5–8.2, with production of marked calcium carbonate precipitations in the medium, while scanty or no precipitations were seen in anaërobically grown cultures, in the presence of a less alkaline pH of the medium. The addition of fermentable sugar on the other hand caused an acidification of the medium and inhibited the production of calcium precipitations. While he considers the change in the pH of the medium the most important factor for the production of calcium precipitations, he believes that the access of carbon dioxide from the air supports their formation, as he observed that filter paper placed on the surface of aërobically grown actinomyces becomes heavily incrustated with calcium salts, obtaining thereby a condition which has a certain similarity to the veil-like membranes covering some of our cultures.

As to the cause or causes of the alkalization of the medium in aërobically treated cultures, the escape of carbon dioxide from the medium, tending to make it more alkaline, can scarcely account for the large change observed. The formation of rings on the other hand suggests the possibility that the enzymatic activity in the presence of living or dead cells plays a part in the changes of the reaction of the medium and probably also in the physico-chemical constitution and composition of its constituents, both of which may contribute to the production of calcium precipitations as noted above. The question, whether the proteolytic activity of the proteases present is involved in this process, cannot be decided with the experimental evidence available. Naeslund suggested the existence of such an interrelation as he found a parallelism between the alkalization of the medium and the proteolytic activity of the actinomyces. Further investigation would be necessary to determine the chemical character and reaction of the end-products of protein degradation in aërobically and anaërobically grown cultures and their effect upon the pH of the medium, especially in regard to malignant growth, as the conditions present in the aërobic cultures are certainly more comparable to the conditions *in vivo* than those existing in the anaërobic type. It appears certain, however, that the lactic acid generated by the tissues kept under anaërobic conditions prevents the production or counteracts the effect of the basic substances produced. The different types of precipitations strongly suggest, however, that various factors participate in their production and are apparently not the same nor active in all of them.

Conclusions. The formation of calcium precipitations in tissue cultures apparently does not depend upon the generation of excessive amounts of lactic acid.

Calcium precipitations have been observed in Carrel flask cultures in which the supernatant fluid had a definitely alkaline reaction (pH 8.2–9.0).

An alkalization of the supernatant fluid and the plasma medium occurs regularly in cultures of normal and malignant cells grown under aërobic conditions, while an acidification is observed, if the cultures are kept under more or less anaërobic conditions.

The cause or causes for the alkalization of the medium are not definitely known. The escape of carbon dioxid from the medium can account for only a minor part of the change observed.

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TYPHOID VACCINE IN THE TREATMENT OF CHOREA.

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THE problem of estimating the value of a new method of treatment of chorea is a rather difficult one. Several factors contribute to this difficulty. In the first place, the variability of the natural course of the disease must be kept in mind. It is well known that the ordinary form of chorea tends to spontaneous recovery in from 6 to 10 weeks; exceptionally, it may last 3 or 4 months. Furthermore, not only is there a great variation in the duration of the disease, but also in the severity. Many cases that seem severe at the outset may respond to the ordinary methods of therapy very quickly, while other cases that begin insidiously may be very resistant to treatment. The difficulty in evaluating a new method of therapy is further enhanced by the fact that the patients who are admitted to the hospital may be in the beginning, the middle or at the very end of their attack. It is obvious, therefore, that a therapeutic agent applied in the latter cases would be a very poor criterion as to the efficacy of this agent. In drawing our conclusions we, therefore, took full cognizance of those factors. Anyone who watched our patients with chorea and their response to the treatment could not help being impressed with the prompt and

frequently sudden recovery that followed the introduction of this method of treatment.

It has been repeatedly observed that the course of chorea is sometimes favorably influenced by an intercurrent fever. It is for this reason that non-specific therapy with resulting febrile reactions was introduced into the management of chorea. Horton¹ reported 2 cases of chorea treated by the intravenous injections of a chemically pure protein. This protein was prepared from ox-blood fibrin by peptic and hydrochloric acid digestion. He claimed that his results were good, although the number of cases was very small, and he attributed the favorable effect to the foreign protein only. Mas de Ayala² treated a boy, aged 12 years, with chorea by provoking an experimental relapsing fever by the inoculation with *Treponema hispanicus*. In that particular case all previous treatment such as isolation, rest and the administration of arsenicals had failed. The chorea became progressively worse for a period of 2 years, so that the boy finally was unable to walk. The induced relapsing fever consisted of 4 febrile attacks, and after the second one the patient began to improve. Total and permanent recovery was produced after the 4th febrile attack. Brown, Smith and Phillips³ reported a series of 23 cases of chorea treated by autoserum injections, intraspinally. Of these, 77 per cent made a complete recovery. Charney⁴ reported 2 cases of chorea treated by Small's anti-streptococcic serum, with no improvement. Similarly, Williams⁵ reported 2 cases treated by the same method with no improvement. Von Kern⁶ reported 3 cases of very severe chorea which recovered soon after receiving 3 to 4 intramuscular injections of 5 to 10 cc. of milk at 3- to 4-day intervals. Following the first and second injections, there was some increase in the choreic movements; then a definite subsidence followed the third or fourth injection. Hymanson⁷ used boiled milk injections in 7 cases of chorea. Of these cases, 4 showed no reaction to the injection and yet they improved remarkably, showing, he stated, that reactions were not necessarily desirable. The 3 cases, however, that showed the most striking improvement developed a pronounced reaction to the milk injection. Nirvanol or phenyl-ethyl-hydantoin, a more recently introduced therapeutic agent in chorea, certainly acts, not so much because of its sedative effect, but because of the shock or febrile reaction that takes place anywhere from 7 to 12 days after the administration of the drug is begun. Sutton,⁸ who first reported the use of typhoid vaccine in the treatment of chorea, states that she came to use it because she wanted to induce a febrile reaction. The desirability of this febrile reaction in the treatment of chorea suggested itself to her when a patient with chorea, who was getting phenolbarbital, improved after developing a barbitol reaction associated with fever. She was not the first one, however, to observe the value of the typhoid fever reaction in chorea. Twenty-five

years ago a Roumanian physician, Mor Turnovszky,⁹ reported a case of chorea which was cured by an intercurrent attack of typhoid fever. He, however, took no advantage of this observation and did not follow up any further cases.

Our method consisted in injecting intravenously a mixture of typhoid, paratyphoid A and paratyphoid B vaccine, each cubic centimeter containing 500,000,000 of typhoid, 250,000,000 of each paratyphoid A and B organisms. The initial dose was anywhere from 0.15 to 0.2 cc. Very soon afterward the child developed a definite and marked chill, followed by a rise in temperature which reached its peak in about 3 to 4 hours, and was usually down to normal in 6 to 8 and occasionally 10 to 12 hours. Most patients would have a sharp reaction of this type following the initial dose but would not react thereafter unless the dose was increased, and this was usually done in amounts of 0.1 cc. per injection per day. However, when the patient did not react to the initial dose of 0.15 to 0.2 cc., or to an increase of 0.1 cc. per day, then the increase in dosage was made more rapidly. We have had cases, however, that reacted sharply to the same dose daily, that is, to a dose of 0.2 cc., and in those cases no daily increase in dosage was made. In a few patients we noticed a secondary rise in temperature the day after the injection. Where that occurred, we either delayed for 24 hours the next succeeding injection, or we did not increase the dose of the injection on that day and, instead, used the same dose that was used on the previous day. The injections would be continued daily, usually for 6 or 7 days, when a rest period of several days would be instituted. Where the child did not recover completely after the first series of 6 or 7 injections, a second, third or even fourth series of injections would be instituted. A decided benefit from the injections was usually observed very soon after the second or third injection, and frequently there would be a complete disappearance of the choreic symptoms before the first series of 6 or 7 injections was completed. The usual rise in temperature was between 102° and 104° F. Where the reaction was very severe and the rise in temperature a very high one, then the same dose was given the next day, or the increase in dosage was only 0.05 cc. instead of 0.1 cc. We have noticed that the cessation of choreic movements did not occur as rapidly in those patients who did not have a marked febrile reaction following the injection of the vaccine. In cases of this type we resorted to a much larger dose, in 1 patient using as much as 1.5 cc. of the vaccine in the final injection.

No untoward effects were observed from this form of therapy in 23 patients who received a total of 297 injections. There was a slight loss of weight because of the temporarily induced anorexia as a result of the fever, but this was gained back very quickly as soon as the injections were stopped. We could discern neither ill-effects nor beneficial effects from the "typhoid shock" upon an

accompanying endocarditis, of which we had 3 cases. Whenever a rapid pulse existed before the vaccine treatment was undertaken, the tachycardia was still present after the effects of the typhoid reaction subsided. The increased pulse rate which accompanied the high rise in temperature following the vaccine administration was in proportion to the rise in temperature. Hench,¹⁰ who studied the reactions to injections of typhoid vaccine intravenously for other conditions than chorea in about 2500 patients, representing an aggregate of about 10,000 injections, found that the reactions were in general well borne, and that unusual reactions were rare. In his series they occurred in 14 cases, an incidence of about 0.5 per cent of the patients. The unusual reactions that he noted were as follows: acute and subacute appendicitis, cholecystitis, enteritis, pleurisy, pericarditis, iritis, glaucoma, adenitis, extensive vascular thrombosis and renal insufficiency. We noticed absolutely no complications nor deleterious reactions. The recovery from the "shock" was, as a rule, prompt and complete.

We studied 23 patients, 11 boys and 12 girls. The oldest child was 12 and the youngest 4, the average age being $8\frac{1}{2}$ years. We divided them, from the point of view of duration, into acute, subchronic and chronic cases; the acute were those who suffered from the disease up to 2 weeks before therapy was begun; the subchronic, up to 6 months; the chronic, over 6 months. Of these patients, 9 (40 per cent) suffered from chronic chorea, in whom the average duration of the chorea was about $4\frac{1}{2}$ years; 6 patients suffered from subchronic, with an average duration of about 4 months; 8 cases were of the acute type, in which the duration of the disease was on an average 11 days before admission to the hospital. Only 3 of the 23 patients had cardiac complications of the mitral type. It is rather significant that the majority of the patients had a low leukocyte count, and some even a leukopenia, before treatment was begun. This finding was the same in the chronic as well as in the subchronic and acute cases. Of the 23 cases, 11 had a leukocyte count of 8000 or over. The average white blood cell count of the remaining 12 cases was 5800, a definite leukopenia. The average white blood cell count on admission for the total 23 cases of chorea was 7500.

Of the 23 cases, 19 were entirely well at the time of discharge from the hospital. In 1 case of chronic chorea there was only a persistent talkativeness, but all other signs and symptoms were gone. One chronic case showed a persistent blinking, and 1 subchronic case was transferred to another hospital because of an intercurrent infection soon after the course of injections was completed. Only 1 of the 23 cases, a subchronic one, was definitely refractory to treatment, the twitchings and irregular movements persisting in spite of the treatment; however, on follow-up examination, 3 months later, this patient was entirely symptom-free.

TABLE 1.—RÉSUMÉ OF ESSENTIAL FINDINGS IN 23 CASES.

Case No.	Name.	Sex.	Age, yrs.	Past history.	Chief complaint.	Duration of illness before treatment.	Physical findings.	White blood cell count.	Number of admissions.	Previous treatment and result.	Number of series of injections.	Total number of injections.	Total amount of vaccine received.	Condition on discharge.	Remarks.
1	J. C.	M.	10	Measles	Twitching	Over 1 yr.	Irregular movements of all extremities; organic systolic murmur in mitral area	5800 and 3000 Av. 4400	3	Discharged unimproved after 6 wks. in hosp.; 2d admission, rest in bed and various drugs gave no relief; given 3 injections of vaccine, 0.2 cc. each; improvement but still some residual twitchings on discharge	5	20	Cc. 7.55	Symptom-free	Steady and continuous improvement after injections were begun.
2	H. G.	F.	9	Measles, tonsillitis; "heart trouble" for past 2 years	Chorea and mitral valve disease	4 mos.	Could not sit quietly; kept moving head and hands; thin and pale and definite evidence of mitral and early myocardial disease	9700	1	Not known	1	7	1.40	Symptom-free	After 7th injection only a few irregular movements; chorea disappeared in 1 mo. and did not recur during 6 wks.' observation.
3	E. T.	F.	12	Constant irreg. movements of extremities and tossing in bed	1 wk.	Neg. except for chorea and slight sec. anemia	Av. 7500	1	None	1	7	1.40	Symptom-free	Movements subsided after 7 injections; no recurrence during 2 mos.' observation.
4	R. M.	M.	10	Nervous and twitching; unable to study; wriggling constantly and twitching of mouth and chewing of tongue	1 yr.	Moderate sec. anemia; heart neg.; typical choreiform movement	Av. 10,600	2	After 8 injections, 0.2 cc. each, restlessness disappeared but least excitement caused jerky movements; 6 more injections, 0.2 cc. each, produced still more improvement but a residual jerking when excited	3	19	4.00	Only slight improvement	Only refractory case in entire series of patients.

5	M. G.	F.	11	Measles, tonsillitis; T. and A. 2 yrs. ago	Shaking and dropping of articles; gradually getting worse; loses temper easily and becomes excited very rapidly; last 2 wks. much worse	3 mos.	Neg. except for choreiform movements	5300	1	Not known	1	11	2.00	Symptom-free	After 5th injection considerable improvement; chorea stopped after 10th injection.
6	J. G.	F.	9	Measles, chickenpox, whooping cough	Constant restlessness; difficulty in talking; jerky movements; paralysis of left arm and left leg	Definite history not obtainable	Choreo movements; flaccid palsy of left side of face, left arm and left leg; unable to talk or walk; decided sec. anemia	6900	1	Not known	2	19	3.00	Palsy disappeared and marked improvement in choreic symptoms	Mother had rheumatism and "heart trouble" when young; sister had chorea; observations were stopped by development of contagious disease.
7	M. S.	M.	11	Measles, mumps, pertussis, varicella and scarlet fever, rheumatism fever, tonsillitis	Marked generalized twitching	4 yrs.	Chorea; functional systolic cardiac murmur; no anemia	7400	2	After 5 injections, 0.3 cc. each, through 11 days, symptoms subsided entirely; 2 wks. later recurrence of some twitching of face and hands	2	11	3.15	No twitching, persistent occasional blinking of eyes	
8	G. D.	M.	11	Measles, pertussis and varicella	Twitchings of face and arms	1 yr. (second attack)	Chorea; no cardiac involvement; moderate sec. anemia; stool examination neg. for ova and parasites	5300	1	First attack 6 yrs. ago; after elimination of seat worms chorea disappeared; second attack, unimproved despite varied therapy, including circumcision	1	5	1.00	Symptom-free	Chorea disappeared after 5 injections; observed for 3 wks. without recurrence of symptoms.
9	J. G.	M.	10	Measles, pertussis, mumps, varicella, tonsillitis	Nervousness; shrugging of shoulders; wrinkling of face; spells of irritability	6 mos.	Neg. aside from choreic symptoms	5700	1	Watched in ward for a week, without any treatment while movements continued	1	7	1.35	Symptom-free	Twitchings stopped after 9 days of vaccine therapy; no return of symptoms during more than 3 mos. observation.
10	F. O.	F.	6	Measles	Twitching of shoulders; rolling of eyes; inability to write because pen suddenly jerks off paper	7 mos.	General condition good except for severe chorea	8000	1	Not known	2	19	5.00	Symptom-free	Mother had chorea; 8 days after admission twitchings improved; movements ceased after 16 days.
11	J. I.	M.	7	Smallpox, measles and rheum. fever; 3 yrs. ago had automobile accident and 3 days after irreg. movements and grimaces developed; tonsils removed but twitchings continued	Very talkative, constant facial grimaces and generalized restlessness off and on; unable to sleep and violent temper	3 yrs.	Normal heart; no anemia; marked chorea	6600	1	Not known	1	11	2.20	All symptoms cleared up except talkativeness	Only patient who developed a febrile reaction but no chill following the vaccine injections.

TABLE 1.—RÉSUMÉ OF ESSENTIAL FINDINGS IN 23 CASES.—Continued.

Case No.	Name.	Sex.	Age, yrs.	Past history.	Chief complaint.	Duration of illness before treatment.	Physical findings.	White blood cell count.	Number of admissions.	Previous treatment and result.	Number of series of injections.	Total number of injections.	Total amount of vaccine received.	Condition on discharge.	Remarks.
12	V. N.	F.	4	Twitching, nervous and fidgety, esp. in past week; would not eat and always appeared tired; spilled food because of shaking of hands	2 wks.	Moderate sec. anemia; marked chorea	3300	1	None	4	24	Cc. 10.60	Symptom-free	
13	B. C.	F.	6	General twitching with pain about heart; beginning of slight twitching of left arm, spread to left leg and soon became generalized	12 days	Mitral disease; choreiform movements	10,600	1	None	2	12	7.30	Symptom-free	Unchanged after 1st series; rest 2 wks.; choreiform movements, after 2d series completed, stopped sharply.
14	R. D.	F.	9	Diphtheria, measles, mumps, pertussis, bronchopneumonia, frequent sore throat and colds	Jerky movements; drags foot and throws hands around	6 yrs.	Normal aside from chorea	10,200	1	Treated repeatedly by medication and rest, without any improvement	2	12	3.45	Symptom-free	No change after 1st series; rest 9 days; 3 days following completion of 2d series chorea stopped; no recurrence during 27 days' observation.
15	M. L.	M.	8	Choreic movements	2 yrs.	No cardiac involvement; chorea	...	1	Rest in bed for 3 wks. but no relief from symptoms	2	14	4.24	Symptom-free	Movements disappeared for 12 days; after 2d series disappeared entirely.
16	J. W.	M.	11	First attack of chorea 6 yrs. ago; constantly getting worse	Consid. facial grimaces; difficulty in walking; talking; inability to eat; one of our worst cases	6 yrs.	Slight sec. anemia; neg. except for severe jerking of extremities, grimaces, inability to talk, eat or walk; quite uncontrollable	9200	1	For 64 days given complete isolation, salicylates, bromids, luminal, codoin and morphin, without any effect on condition	2	16	1.04	Symptom-free	Striking therapeutic gain; 6 days after vaccination was begun, first definite improvement and lessening of speech defect; 27 days after, movements subsided entirely, and remained well for 37 days' observation.

17	F. C.	F.	10	Varicella, measles and pertussis	Jerking and twitches	5 days	Neg. aside from chorea	9500	1	None	2	29	15.40	Symptom-free	Definite improvement following each "vaccine shock," at end of 50 days' hospitalization, was discharged cured.
18	E. W.	M.	10	Rheumatic fever, 4 and 3 yrs. before admission; measles	Spasms and twitches	17 days	Enlarged tonsils; loud systolic murmur in mitral area	...	1	Treated in usual way, without improvement	1	6	1.20	Symptom-free; murmur disappeared as choreic movements subsided	Within 8 days after 1st injection patient improved and injections were stopped.
19	H. W.	F.	11	Measles, mumps and varicella; T. and A. 5 yrs. before present illness	Nervous and irregular movements steadily worse; unable to sit still	2 mos.	Neg. except for chorea	8000	1	Not known	1	12	2.40	Considerable improvement	Within 15 days after injections were begun, considerable improvement noted.
20	T. W.	M.	10	Spasmodic jerking of muscles, continually growing worse	13 wks.	Loud systolic murmur in aortic area; severe chorea	10,800	1	Not known	1	11	2.20	Symptom-free; murmur disappeared as movements subsided	Marked improvement after 6th injection.
21	D. S.	F.	10	Scarlet fever, diphtheria, measles, varicella, pertussis and frequent sore throat, colds	Twitchings	6 yrs.	Neg. except for chorea	9000	1	Not known	1	9	1.80	Symptom-free	Definite improvement after 5th injection.
22	L. L.	F.	9	Measles, mumps and chickenpox; T. and A. at 4 yrs. of age	Continuous twitches of mouth and facial muscles; considerable and constant irregular movements of arms and legs	Definite history not obtainable	Neg. except for chorea	6800	1	Received Snell's S.C.A. vac. and sympt. were definitely aggravated; put on bromids, lun-inal, acetyl salicylic acid, antipyrin, salicylates and kept at absolute rest; these measures continued for 33 days, with no improvement whatsoever	1	8	1.60	Symptom-free	After 3d injection, settled down and rested quietly; 10 days after vaccination therapy was begun, movements disappeared altogether; was discharged cured after 15 days from beginning of the vaccination therapy.
23	S. S.	F.	8	Tonsillitis, whooping cough, cervical adenopathy	Twitching; nervousness; restlessness and tossing about of left upper extremity; peculiar speech	2 wks.	Malnutrition; diseased tonsils; marked cervical adenopathy; soft systolic murmur was heard over entire precordium	9000	1	None	1	8	2.80	Marked improvement	

Cases 1 to 15 studied at Jefferson, 16 to 21 at St. Christopher's, 22 at Memorial and 23 at Jewish Hospitals.

The most significant fact to be emphasized in this study is the remarkable effect of this form of therapy on the chronic cases. Of the 9 chronic cases in which the chorea had persisted on an average of $4\frac{1}{2}$ years, 8 became entirely symptom-free and 1 showed only a persistent blinking of the eyes at the time of discharge from the hospital.

There are several criteria by which we may measure the efficacy of a new method of treatment of chorea: (1) The rapidity of the disappearance of the symptoms; (2) whether or not the patients continue to be free from choreic movements after the treatment is stopped; (3) whether or not the new method, in comparison to the older forms of treatment, shortens the hospitalization period; (4) in what percentage of the cases, if any, there is a recurrence of the chorea. We were quite struck by the marked rapidity with which the symptoms of chorea disappeared following the vaccine injections. We were able to continue our observation on the patients for quite a while following the cessation of therapy, because at the time of our study we were not interested in the third criterion, namely, the length of the hospitalization period. Many of the patients were kept in the hospital for a period of 1 and 2 months in order to observe them further and watch for any recurrence of the symptoms. Several of the patients went home and returned later for the removal of tonsils and adenoids, and they were still free from choreiform movements. Two of the cases were readmitted at a later date on account of the cardiac condition, and they also showed no evidence of recurrence of the chorea.

Eleven patients returned for follow-up examination. The findings are summarized in Table 2. As will be discerned, out of the 11 cases, 9 were chronic, 1 subchronic and 1 acute. The patients were reexamined 3 to 15 months following their discharge from the hospital. Of the 9 chronic cases, 5 were entirely well; the 1 subchronic and 1 acute case were well; of the 4 remaining chronic cases, 1 only showed a certain amount of general restlessness but no actual twitching, and the remaining 3 a recurrence of choreiform movements. Out of 11 cases possibly 7 or 8 were therefore still free from choreiform symptoms upon reexamination 3 to 15 months later, in spite of the fact that 6 of them were chronic choreic patients and had been suffering from chorea an average duration of over 4 years prior to the time when vaccino-therapy was started.

Discussion. The majority of observers that reported favorably on the effectiveness of nirvanol in the treatment of chorea consider that its use is not justifiable on account of the severe and dangerous reactions which may follow, and which are neither predictable nor preventable. Pilcher and Gerstenberger,¹¹ in reporting on their results with nirvanol, state that the complications usually consist of "irritation of the mucous membranes, stomatitis, conjunctivitis, edema of the face, and urticaria and, rarely, vulvovaginitis, balanitis and irritation of the urinary tract with bloody urine. In 1 case

TABLE 2.—FOLLOW-UP EXAMINATIONS OF 11 CASES OF CHOREA.

Case No.	Name.	Type of case.	Time elapsed since discharge from hospital.	Condition at present.	Remarks.
1	J. C.	Chronic	7 mos.	Well	
2	H. G.	Subchronic	4 mos.	Well	Marked impr. of heart; mitral disease still present.
4	R. M.	Subchronic	3 mos.	Well	Shows complete recovery, though refractory when discharged.
7	M. S.	Chronic	14 mos.	Irreg. movements of head and eyes	
8	G. D.	Chronic	15 mos.	Well	
9	J. D.	Chronic	10 mos.	Well until 6 weeks ago occ. twitching of nose and blinking began	
10	F. O.	Chronic	4 mos.	Well	
11	J. I.	Chronic	11 mos.	Chr. blepharitis and chr. rhinitis; occ. blinking due to blepharitis	W.B.C., March 9, 1933, 7100.
12	V. N.	Acute	9 mos.	Well	W.B.C., August 31, 1932, 3700; January 7, 1933, 8800.
14	R. D.	Chronic	6 mos.	Twitching of face; irreg. movements of hands, recurring 1 month ago	
15	M. L.	Chronic	3 mos.	Some restlessness but no definite twitchings	

there was exudation into the lungs, resembling pneumonia." Feer¹² observed a boy with chorea who developed the alarming syndrome of agranulocytic angina following the usual dose of nirvanol for chorea. This boy eventually recovered. In rabbits large doses led to exhaustion of the bone marrow and agranulocytosis. These disturbing symptoms or complications have never been observed in the 23 cases that we hereby report on the use of typhoid vaccine in the treatment of chorea, nor have they been mentioned by Sutton⁸ nor reported by Hench¹⁰ in his studies on the reactions to injections of typhoid vaccine for other conditions than chorea. Furthermore, nirvanol seems to be most effective in the first attack or in acute chorea, whereas typhoid vaccine has been found by us to be most valuable, particularly in chronic chorea, that is, those cases that are usually obstinate in character, baffle all therapeutic

attempts, and are resistant to every possible measure ordinarily undertaken for the relief of the condition.

Summary. Twenty-three cases of chorea, 9 of which were chronic, were treated by means of typhoid-paratyphoid vaccine, intravenously; 19 were entirely symptom-free at the time of discharge from the hospital. Of the 9 chronic cases in whom the average duration of the symptoms was $4\frac{1}{2}$ years, 1 showed a persistent talkativeness and 1 a persistent blinking of the eyes, but all other symptoms had disappeared. One patient who suffered from chorea for 2 months was improved following the vaccine injections, but we were unable to continue our observations on her because of transfer to another hospital soon after the injections were completed. Only 1 of the 23 patients, a subchronic one, was definitely refractory, and the twitchings and irregular movements persisted in spite of the treatment; nevertheless, when this patient returned 3 months later for follow-up examination he was entirely well. A reëxamination of 11 cases, 3 to 15 months subsequent to discharge, showed 7 and possibly 8 to be entirely well, in spite of the fact that over 50 per cent of them belonged to the class of chronic chorea. No untoward effects were noticed in any of the patients from the vaccine injections. While the number of cases is not very large, nevertheless the uniformity of favorable results points to this procedure as a valuable method in the treatment of chorea, and its effectiveness is especially emphasized in the obstinate and chronic cases.

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SPONTANEOUS RUPTURE OF THE ESOPHAGUS WITH A REPORT OF FOUR CASES.

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SINCE the death of Baron Wassenau (1724), attributed by Boerhaave to spontaneous rupture of the esophagus, approximately 40 cases have been reported. It is the purpose of this paper to

submit a brief review of the literature on this subject, to report 4 cases occurring at the Louisville City Hospital and to suggest a few general conclusions regarding this condition.

Fitz¹ (1877), made a complete survey of all the literature on this subject. He concluded that the findings in many of the reported cases were really due to postmortem changes and that in others there was definite evidence of preëxisting disease. He accepted the cases of Allen, Meyer, and Grammatski as being actual spontaneous ruptures occurring in previously healthy esophagi. He explained the rupture, hemoptysis, and subcutaneous emphysema as being a result of straining to expel a foreign body in the esophagus, and attributed the symptom complex and early death to irritation of the vagus and sympathetic nerves, and if prolonged, to gangrene of the mediastinum and lung.

Ziemssen² (1878) and MacKenzie³ (1884) stretched esophagi removed from fresh cadavers with weights, and found that an average of 7 to 8 kilograms was required to rupture the muscularis, while about 10 kilograms were necessary to rupture the mucosa. MacKenzie also produced rupture by exerting 5 to 11 pounds of water pressure within the esophagi.

Brosch⁴ (1900), by using water pressure from within—in esophagi removed from fresh cadavers—was able to produce linear rupture of the tubes, always below the point of bifurcation of the trachea, and, in a majority of cases, near and including the cardiac sphincter. In these cases the mucosa was the part first torn. He treated the mucosa of 6 cases with gastric juices at body temperature over periods of 12 to 48 hours. In 4 of these, approximately the same force was required to produce rupture as in the untreated cases. Of the 2 remaining, it is particularly interesting that in 1, a case dying of cerebral abscess in which there was said to have been a contracture of the cardiac sphincter, spontaneous rupture occurred after 35 to 40 hours. Brosch concluded that spontaneous ruptures of the esophagus would occur following emesis, due either to the act (increased intra-esophageal pressure), or secondarily, due to digestion by the gastric juice made possible by the presence of ulceration.

Williams and Boyd (1926), made a linear incision through the lower portion of the esophagus in dogs and then induced vomiting in the animals. Postmortem examination of these animals did not reveal the gross and microscopic changes described in the reported cases and they concluded that spontaneous rupture of the esophagus is preceded by inflammatory changes which weaken the wall.

The following case reports constitute all those recognized at the Louisville City Hospital during the past 10 years, excluding instances of rupture associated with obvious lesions, such as aneurysm or neoplasm.

Case Reports. CASE 1.—Female, white, aged 47 years, admitted November 1, 1931. Two hours prior to admission, following what was

described as an average evening meal, the patient became nauseated and vomited. After vomiting she seemed somewhat relieved but after a few minutes vomited again. At this time she suddenly complained of excruciating pain in the lower mid-portion of her chest and cried that she was going to die. She vomited and coughed up a small amount of blood. She was seen promptly by her family physician, who gave her $\frac{1}{4}$ grain morphin and sent her to the hospital. Previous history was negative except that she had been taking injection treatments for varicose veins for a few weeks prior to admission, having received 4 treatments in all, the last having been about 5 days before. She was said to have been treated several years previously for "heart trouble" but no symptoms could be elicited to support this diagnosis.

Examination revealed a moderately obese white female, aged 47, who was slightly cyanotic, dyspneic, very apprehensive, and obviously critically ill. Her temperature was 97°, pulse 112, respiration 30, and blood pressure 120/70. There was slight subcutaneous emphysema over the lower anterior portion of the neck. Occasional fine inspiratory râles could be heard at both lung bases. There was slight tenderness to deep pressure in the epigastrium. Both legs showed moderate varicosities.

She was kept reasonably comfortable during the next 24 hours with $1\frac{1}{2}$ grains morphin and the use of an oxygen tent. There was slight increase in the subcutaneous emphysema of the neck.

On the 4th day the subcutaneous emphysema—which had involved the face and upper thorax—began to diminish. Findings in the left base were suggestive of beginning bronchopneumonia. The patient was getting nothing by mouth, and glucose and saline were being given intravenously and subcutaneously.

On the 7th day findings in the lower part of the left chest were consistent with fluid, the presence of which was verified by Roentgen ray. About 75 cc. of dark brown fluid with a granular sediment were removed by thoracentesis. This fluid had a very offensive odor, quite similar to the odor of the gas frequently eructated by the patient. She was seen at this time by Dr. August French, Resident in Surgery, who made the diagnosis of ruptured esophagus. The fluid obtained from the thoracic cavity contained free HCl and on culture produced *S. aureus* and *albus*, *B. mucosus capsulatus*, *B. subtilis*, *Lepthothrix buccalis*, and a Gram-negative coccoid bacillus.

On the 10th day a thoracotomy was performed and 2 drainage tubes inserted. There was moderate drainage of brownish fluid—similar to that obtained on thoracentesis—for the next 48 hours and the pleural cavity was irrigated with normal saline.

On the 13th day 150 cc. sterile water containing carmine dye were given by mouth. This appeared in the drainage tubes after about 2 hours.

During the next 4 days the patient became gradually weaker and expired on the 17th day of her illness.

Autopsy (Extract). In the lower part of the chest at the left posterior axillary line is a thoracotomy wound in which there are 2 rubber drains.

The left pleural cavity contains air, the lung being collapsed. Both the parietal and visceral pleura are covered by fibrino-purulent exudate. The rubber drains extend well into the dependent part of the cavity. The right pleural cavity contains about 100 cc. of clear, straw-colored fluid.

The esophagus is opened in its lower portion anteriorly and there is found to be a rent measuring 7 cm. in the left lateral portion of its wall opening directly into the pleural cavity. This rent extends from 6 cm. above the cardia through the cardia and dissects the wall of the stomach in pouch-like fashion 2 cm. below the cardia, but does not open into the abdominal cavity.

Microscopy. Several sections are taken from the wall of the rent in the esophagus. There is some recent blood clot attached to the surface of the tear. It is lined by granulation tissue, the deepest portion of which is quite well formed. The leukocytic infiltration is moderate, and consists of quite a number of plasma cells and lymphocytes. There are also some endothelial leukocytes and in some areas polymorphonuclears, though these are surprisingly few. The vascular supply of the granulation tissue is abundant and seems consistent with the inflammatory reaction. The epithelium ends abruptly at the edge of the ulcer. Inflammatory reaction extends back under it for a short distance. There is no microscopic evidence of a previously existing ulcer. The arteries and arterioles of the region are for the most part well preserved. Some of them are slightly damaged. Close to the granulation tissue, in fact in the base of it, two vessels are seen which have occluded lumina. These were probably not previously thrombosed; the walls do not indicate a long standing inflammation or sclerosis. It is quite possible that this occlusion has occurred after the rupture of the esophagus. In other words, it does not seem that the organization in the lumen of the vessels is old enough to warrant the interpretation that the wall was weakened by this vessel occlusion and, therefore, ruptured. This organization is recent and very probably the result of the tear, rather than the cause of it.

Summary of Case. The patient's death is attributed to the effects of pleurisy, caused by rupture of the esophagus. The shape of the esophageal tear indicates a mechanical factor in its occurrence. The microscopy of this lesion is consistent with the history that it occurred 17 days before death.

CASE 2.—Female, colored, aged 52 years. Admitted January 20, 1930. The patient was brought to the hospital in a comatose condition. No reliable history could be obtained. Her son said that she had apparently been in good health up until 3 days prior to admission. At this time she developed a slight "head cold" which became worse. She had a moderate cough, seemed feverish, and was thought to have had one chill. During the 24 hours prior to admission her condition became much worse, she became delirious and hospitalization was advised by a private physician.

Examination revealed a well developed and well nourished colored female, aged 52, who was comatose and obviously moribund. Her temperature was 95°, respiration 60, pulse 180, and blood pressure 60/30.

There was slight drawing of the facial muscles on the left side. The right pupil was smaller than the left; both reacted to light. Her teeth were dirty and carious. There was definite dullness to percussion over the lower third of the chest posteriorly on the left side. Over this area there was a pleural rub. Breath sounds were distant and chiefly bronchovesicular in type. Crepitant râles were present on inspiration. Her extremities were flaccid, tendon reflexes were sluggish, and no abnormal reflexes could be elicited.

The patient did not respond to stimulants and died shortly after arriving in the ward.

Autopsy (Extract). The left pleural cavity contains approximately 350 cc. of reddish, slimy, turbid material which looks as though it contained some purulent exudate. There are no adhesions. The tissues of the mediastinum are dark brown in color.

The left lung contains practically no air. Sectioning reveals atelectasis and congestion to a marked degree on left side.

The esophagus is found to have an elliptical opening running longitudinally on its left anterior aspect about 2 cm. in length extending upward from the level of the diaphragm. The remaining gastro-intestinal tract is negative with the exception of a healed ulcer about 2 cm. distal to the pyloric sphincter.

After removal of the skull cap there is a marked flow of spinal fluid.

There is considerable yellow purulent exudate over the base of the brain. This is most marked around the brain stem. The convolutions are slightly flattened.

Bacteriology. Smears of the meningeal exudate show a Gram-negative intracellular diplococcus, morphologically a meningococcus.

Microscopy. Sections taken from the lesion in the esophagus show a surprisingly small amount of acute inflammatory reaction. This consists only of degeneration and edema. Some of the larger vessels, that is, small arteries larger than arterioles, are moderately damaged by proliferation of the intima. It is estimated that this encroachment on the lumen consists of $\frac{1}{4}$ to $\frac{1}{3}$ of the diameter. Some of the smaller vessels, such as arterioles, are likewise damaged and the encroachment on their lumina is slightly greater; estimated to be $\frac{1}{2}$ in some instances. No vessels are seen which are entirely closed, except for a few in the mucosa. Some of these are possibly entirely closed. The muscle cells are slightly atrophic. There is some hyalin degeneration of the stroma in the submucosa. There is some lymphocytic infiltration about the mucous glands. One lymphatic is seen which is plugged with leukocytes, most of which are polymorphonuclears. Some of the mucous glands are slightly stained with secretion. In 1 of the sections there is a bit of lymphoid tissue. This is probably a normal structure. There is some scarring about some of the mucous glands in the submucosa. This scar tissue is hyalinized.

Summary of Case. The cause of death is meningococcic meningitis. The esophagus ruptured a short time before death. The scarring and hyperplasia of the small arteries of the esophagus in the wall of the rent indicate that there was some previous inflammation. The shape of the tear indicates a mechanical factor in its production.

CASE 3.—Female, colored, aged 16 years. Admitted April 1, 1930. The patient came to the hospital complaining chiefly of headache. She said that she had been entirely well until 3 to 4 days previously, at which time she developed a head cold. Two days later she developed soreness and stiffness in her back and neck and felt that she was becoming worse. The headache was described as being very severe, constant, and involving the frontal and occipital regions. Her past health was not remarkable.

Examination revealed a well developed and well nourished colored female, aged 16, who appeared very toxic. Her temperature was 102° , pulse 104, and respiration 28.

The head was retracted and the neck rigid. Her skin was moist and hot. The right pupil was widely dilated, the left about normal in size. Neither reacted to light. Examination of the retinae revealed moderate papillary edema bilaterally. Her tongue and lips were dry and parched. All extremities were spastic, tendon reflexes were hyperactive, and Kernig and Babinski signs were positive.

Spinal puncture revealed a milky fluid under increased pressure which showed ++++ globulin, a 2500 cell count with 95 per cent polymorphonuclears. Primary smear showed Gram-negative intracellular diplococci.

The patient was given antimeningococcic serum into the spinal canal and into the cisterna magna and seemed to improve for the next 3 days. There was some decrease in the muscular spasticity and the patient said she felt much better. During the 3rd night, however, it was noticed that she was having considerable respiratory difficulty and was obviously much worse. Her condition continued critical during the following day and signs were observed in the left lung base which were interpreted as being due to pneumonia. She expired during the night of the 4th day of hospitalization.

Autopsy (Extract). The left pleural cavity contains 350 to 500 cc. of dark brown to black fluid, in which particles of food are found. Pressure is made on the stomach and its contents are seen to flow from a rupture in

the lateral border of the esophagus. The opening measures 61 mm. in length and extends upward from the diaphragm. The margins are not discolored and there is no evidence of necrosis. Two small ulcers are seen in the mucosa. The larger one measures 2 mm. in diameter and has a dirty gray friable base. Both parietal and visceral pleura in contact with the fluid are darkly stained. The connective tissue in the mediastinum is hemorrhagic.

The left lung is crepitant throughout. Sectioned surfaces are pinkish-gray and when scraped, reveal deep red firmer areas, giving a mottled appearance. The right lung is normal.

Examination of the brain reveals extensive thick grayish purulent exudate at the base in the subarachnoid spaces.

Microscopy. Sections taken from the esophageal lesion show recent necrosis of the connective tissue. This is evidently the result of the action of gastric juice. There is no reaction on the part of the tissue. There is no leukocytic infiltration in the wall of the tear. The vessels are well preserved. There is some extravasation of blood. This blood is partly laked. Some of the vessels near the tear are filled with blood which is partly disintegrated, evidently the result of the action of gastric juice. In one of the sections there is a small amount of leukocytic exudate. This is evidently taken from one of the small ulcers mentioned in the gross description. About these areas there are large masses of bacteria in the tissues. These have a varied morphology, none of them can be definitely recognized as meningococci. Most of them are very large rods.

Summary of Case. This patient's condition evidently began as a meningococcic meningitis, which was complicated by a terminal bronchopneumonia and perforation of the esophagus. The esophageal lesion possibly was contributed to by infected emboli. This would account for the small ulcers in the mucosa noted grossly. This interpretation cannot be certain. The histology indicates it is probable. The shape of the tear indicates also that there was a mechanical factor in its production.

CASE 4.—Male, white, aged 60 years. Admitted December 18, 1931. This patient had complained of variable pain in the epigastrium for 2 years. It was said to have been cramping in nature and he was unable to say that food, either in type or quantity, had any definite relation to it. Sometimes he would be symptom-free for several days. At times his discomfort was associated with vomiting, the vomitus said to have consisted of undigested food. The patient had been receiving treatment at the out-patient department during most of this time and a complete work-up was said to have revealed nothing except a questionable duodenal ulcer on Roentgen ray examination. He was referred into the hospital because his improvement had not been satisfactory. His past health was not remarkable. He had used alcohol moderately.

Physical examination revealed a well developed and well nourished white male, aged 60, who appeared in no acute distress. His temperature was 98°, pulse 80, respiration 16 and blood pressure 110/64. His examination was entirely negative except for slight peripheral arteriosclerosis, a senile cataract in the left eye, and slight tenderness to deep pressure in the epigastrium.

A thorough study during 3 weeks revealed nothing except a verification by Roentgen ray of the original impression of duodenal ulcer. All laboratory findings, including gastric analysis, were within normal limits.

There was, however, on 1 Roentgen ray examination, some delay in the emptying of the esophagus which was not present after the use of atropin. Operation was decided upon after a thorough trial with dietary and medicinal measures failed to give the patient satisfactory relief.

On the 25th day of hospitalization under local anesthesia which was later

reinforced by nitrous oxid and a small amount of ether, the duodenal ulcer was excised and a posterior gastro-enterostomy was performed. Considerable adhesions were encountered and the operation required over 3 hours but the patient left the operating room in good condition. The day following operation, his condition became worse. He was slightly cyanotic and vomited about 100 cc. of brownish material. A Levine tube was passed into the stomach and the stomach washed out with tap water. The tube was left in the stomach for constant drainage. His condition continued to become worse during the next day and signs in both lungs were thought indicative of bronchopneumonia. He died at the end of the second day postoperative.

Autopsy (Extract). In the midline of the abdomen there is a recent surgical incision. There is a gastro-enterostomy connecting the pyloric portion of the stomach with the jejunum about 5 cm. from jejunal junction. It is well open.

There are old adhesions binding the lung to the parietal pleura on both sides. On the left side there is brownish, straw-colored fluid approximately 250 cc. in amount. On the left side there is mediastinal emphysema. Examination of the mediastinal tissues reveals dark brownish fluid surrounding the esophagus just above the cardiac sphincter of the stomach. The stomach and esophagus are opened by an anterior longitudinal incision and rupture of 2 esophageal ulcers demonstrated. The bases of the ulcers are thin and dark brown in color. They are about 1 cm. in diameter and lie just above the cardia, one on the right and one on the left side. The stomach contains fluid similar to that found in the mediastinal tissues.

In the right lung there is marked congestion and some consolidation of the middle and lower lobes. There is a small amount of thin fibrinous exudate on the surface of the lower lobe. The left lung is similar in appearance, except for a part of lung adjacent to the brownish area in the mediastinum, which appears to be necrotic.

Microscopy. Sections of the esophageal perforations show them to be lined with necrotic tissue. There is no repair. There is some proliferation of the intima of the small vessels, especially arterioles.

Summary of Case. The patient's death is attributed to bronchopneumonia. The perforation of the 2 esophageal ulcers occurred a short time before death and was undoubtedly a contributing factor. The causes of the ulcers and of the perforations are not demonstrated.

Comment on Case Reports. Case 1 represents, as well as may be determined, spontaneous rupture of a previously normal esophagus.

Cases 2 and 3 represent rupture associated with intracranial lesions. The relative frequency of this occurrence has been commented upon by previous writers. Although a definite history of vomiting is lacking in these 2 cases, its occurrence is assumed since the nature of the tears indicate increased intra-esophageal pressure of considerable degree.

In Cases 2 and 4, the arterial changes may have been factors predisposing to rupture.

Case 4 shows evidence of preëxisting abnormality of the esophagus as evidenced by delayed emptying on Roentgen ray examination. Also, there was a mechanical agent in this case which may have produced ulceration. It is unlikely that the tube could have caused the perforations because of the soft texture of the tube used and the ease with which the stomach was entered and the lavage performed.

General Discussion. It is generally agreed that the exciting cause of spontaneous esophageal rupture is the increased intra-esophageal pressure incident to vomiting. It is questionable whether or not perforation ever occurs simply as a result of ulceration and digestion by gastric juice. As immediate predisposing causes to rupture—spasm, atony due to repeated vomiting, and digestion by gastric juice are undoubtedly all factors and vary with the individual case. Obstruction of the upper part of the tube by spasm, a foreign body (as food), or from any cause, would obviously make rupture more apt to occur.

While there is some controversy as to the rôle played by pre-existing disease in this condition, it is reasonable to assume that anything which would weaken, or interfere with the normal elasticity or motility of the tube, would make it more liable to rupture. It would follow then, that stricture, vascular thrombosis, infarction, cardiospasm, ulceration, esophagitis, and scar formation predispose to rupture. They have probably been factors in some instances of rupture in so-called normal esophagi.

When one considers the exciting and immediate predisposing causes of esophageal rupture, it is not difficult to understand why it occasionally occurs as a complication of other diseases. In those associated with intracranial lesions, in particular, the frequent tendency to violent vomiting and to muscular spasm makes conditions ideal for such an accident. In fact, it seems surprising that it does not occur—or, at least, is not recognized—more often.

While the exact etiology and mechanism of esophageal rupture are not always apparent, the diagnosis of its occurrence should not be difficult. The sudden occurrence of severe excruciating pain in the lower portion of the chest coming on during the act of vomiting and associated with hematemesis, subcutaneous emphysema of the neck, respiratory distress, and marked prostration, justifies a diagnosis of esophageal rupture. This symptom complex was well illustrated in Case 1 and is so consistently present in the reported cases that it may be regarded pathognomonic of ruptured esophagus.

The subcutaneous emphysema is explained by most writers as being caused by air forced into the mediastinum along with the gastric contents. The explanation of the marked prostration and usually rapid death is, as yet, in dispute. The theory of Williams,⁹ 1926, that "death is due to a sudden attack by virulent organisms within an undefended, closed, and toxin-absorptive cavity," seems hardly justified. The organisms thus introduced are mostly non-pathogenic and certainly are of relatively low virulence. Also, the symptoms as observed in Case 1 and as described in the reported cases, are not those of bacterial toxicity, but rather those which would be expected from sudden severe injury to vital structures. It would seem more logical to explain the events by injury to important nerve structures in the mediastinum by the irritation and the

digestive action of the gastric contents as suggested by Fitz¹ and MacKenzie.³ Such an explanation is supported by pathologic findings and accepted physiology. Bacteria are undoubtedly a factor, probably of increasing importance the longer the patient lives.

Unfortunately, the treatment of these cases offers very little encouragement and the prognosis is extremely poor. The forces which produce the rupture expel a quantity of gastric contents into the mediastinum so that the greatest damage has been done and the outcome usually determined before the patient is seen by the physician. Withholding everything by mouth is imperative as was proved by the administration of carmine dye in Case 1. Sedatives, fluids and nutriment subcutaneously and by venoclysis, and oxygen if there is improper oxygenation of the blood, constitute the other major therapeutic measures. Passage of a tube into the stomach might seem indicated, but the dangers incident to such a procedure—such as the chance of increasing the trauma at the site of the lesion—more than offset its indications. The patient's general condition, certainly in Case 1, and apparently in all reported cases, prohibits surgical procedures directed toward repair of the tear or drainage at the site of the rupture. Immediate surgical drainage of the pleural cavity, as suggested by Boyd and Williams,⁹ and urged by Smead,¹⁰ in cases showing rupture into this cavity is not always advisable. In addition to the fact that the patient is a poor risk even for minor surgery, it is not improbable that a great deal of the fluid present in the cavity is produced as a protective exudate and at least early in the condition is actually helpful. It would be better to let the choice of this procedure be determined on the merits of the individual case—being influenced by the patient's general condition and the character of the fluid obtained on thoracentesis. It is significant that there are authentic cases¹² of esophageal rupture with evidence of pleuritis and effusion which have recovered without surgical interference.

Summary and Conclusions. 1. The literature on spontaneous rupture of the esophagus is presented and 4 observed cases are reported.

2. The following conclusions are made regarding this condition:

(a) Esophagitis, stricture, ulceration, cardiospasm, and vascular changes predispose to esophageal rupture. It may occur, however, in normal esophagi.

(b) A sudden onset of pain in the lower portion of the chest, coming on during vomiting, and associated with hematemesis, subcutaneous emphysema of the neck, respiratory distress and prostration, is pathognomonic of esophageal rupture.

(c) The symptom complex and usually early death are due to the irritating and digestive action of the gastric contents on the mediastinal structures and pleura.

(d) Sedatives, withholding everything by mouth, and the administration of fluids and nutriment by venoclysis, proctoclysis, and hypodermoclysis constitute the more important means of treatment. Oxygen is usually indicated. In the cases presenting evidence of pleuritis and effusion, surgical drainage is indicated in selected cases.

(e) The prognosis is always extremely grave.

NOTE.—The descriptions and interpretations of the autopsy findings in the 4 case reports were prepared by Dr. A. J. Miller, Professor of Pathology, University of Louisville School of Medicine.

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AMEBIASIS IN NORTHERN NEW JERSEY.*

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BROWN,¹ summarizing the cases of amebiasis diagnosed at the Mayo Clinic in the 10-year period, 1921–1931, reported 4 cases from New Jersey. These cases constituting 0.29 per cent of the patients seen from this state, indicate a higher percentage incidence than in many of our Southern states, where endamebal infestation is recognized as flourishing. As search fails to reveal any other cases reported from New Jersey, one would be lead to suspect that amebic dysentery is rarely seen here. To call to mind the endemic nature of this disease, its aspect from the point of view of public health and preventative medicine, and of reporting 5 cases seen in private practice within the past year, we present this paper.

That amebiasis exists in endemic and epidemic form in cities in the northern United States is generally recognized. Kaplan *et al.*² report an epidemic in a large hotel in Chicago traced to a kitchen employec who harbored the cysts. Lear and Merrill,³ in 1924, reported an epidemic in a suburb of New Haven, Conn. Stiles⁴ in

* Read before the Academy of Medicine of Northern New Jersey, May, 1933.

1932 stated that of 196 immigrants at Ellis Island 8.6 per cent were infested, and of 2584 American soldiers who did not go to Europe 3.5 per cent were affected. He concluded that the presence of cysts in apparently healthy carriers was common. As early as 1909 Patterson⁵ told of 3 cases of amebic dysentery who had never been outside the New York metropolitan area and again called to notice the cases reported by Musser and Stengel in Philadelphia in 1890 and Stockton in New York in 1894. Brooke and Goodale,⁶ in 1931, reported 5 cases in Massachusetts. Two of these patients had never been out of the temperate zone. In 1916 Sanford⁷ wrote that from 1911 to 1916 that of amebic dysentery at the Mayo Clinic 535 cases had been seen from Northern states and 600 cases from Southern states and the Tropics. None of these cases were Jerseyites but 4 came from New York and 4 from Pennsylvania.

Thus with cases occurring within distance of a Sunday auto ride, in Pennsylvania, New York, Massachusetts, and Connecticut, there is every reason to assume that many cases must exist among us, and we know from personal communications that others have seen these cases though they were not reported.

Craig⁸ believes that 10 per cent is the average incidence of infestation in the United States. He finds that 50 per cent of the carriers complain from time to time of gastro-intestinal symptoms, occasional diarrhea, colicky pain, anorexia, flatulence and, at times, tenderness over the liver, leading to a diagnosis of cholecystitis.

The reported incidence of infested carriers varies greatly. Andrews and Paulson⁹ state that in 502 unselected people, living at home in Baltimore, 10.9 per cent harbored protozoa in the gastro-intestinal tract, of which only 0.2 per cent had cysts of *E. histolytica*, while Kofoid¹⁰ found 10.8 per cent of troops returning from France infested with *E. histolytica*. It was he who estimated that a healthy carrier passed on the average 14 million cysts per day. In our examination of stools we have been able to demonstrate cysts only in patients suffering from dysentery and have seen no healthy carriers.

Case Abstracts. CASE 1.—E. A. E. (referred by Dr. R. W. Tilton), a 40-year-old insurance employee, was a resident of Maplewood, N. J. He suffered from an attack of diarrhea when a soldier in France in 1918 from which, after several weeks of illness, he recovered. He was well until the end of October, 1931 an interval of 13 years. He was seen by us in December 1931 after 6 weeks of continual diarrhea. Physical examination was negative. The liquid stool showed an occasional red blood cell, but no ova. A proctoscopic scraping from the rectal mucosa, examined on a warm slide immediately on removal from the rectum, revealed *E. histolytica* in large numbers. Cure was effected with emetin hypodermically. A check-up on the stools after 1 month revealed no parasites or cysts. This is a case which harbored the parasite for 13 years without apparent symptoms and is similar to the patient reported by Shilling in which he brought up the question of war compensation.

CASE 2.—F. C. B. (referred by Dr. Ripley), a 28-year-old resident of Hackensack, N. J., noted abdominal pain and a looseness of bowel while boating in Florida in 1930. From that time until he was seen by us in 1932 he complained of crampy pains following bowel movements and of

diarrhea. An appendectomy had been performed but afforded no relief. Our proctoscopic examination revealed a slightly congested mucous membrane. His urine contained a trace of albumin and rare granular casts—evidence of a toxic process. His feces were liquid and positive for blood and pus cells. *E. histolytica* were present. He was put on a low residue, high-protein diet and a course of emetin hydrochlorid was instituted. The patient was symptomless by the 7th injection and failed to return for completion of the course.

CASE 3.—C. F. J., aged 40, had a diarrhea of 2 years' duration with blood and mucus appearing daily in his stools. He had had an appendectomy without relief. He was losing weight and seemed to be growing progressively worse. The proctoscope disclosed an ulcerated mucosa, scrapings from which contained what appeared to be dead amebæ. Their morphology was not sufficiently clear to warrant a diagnosis. The stool was liquid and contained blood and pus. No cysts were found. Hopefully 2 series of emetin hydrochlorid were administered at an interval of 2 weeks. This was supplemented by a low residue high-caloric diet. The patient felt better but the diarrhea continued. A second stool left us no better informed than the first examination, but a third stool examination, after several weeks, disclosed numberless cysts of *E. histolytica*. The patient was treated at home. He was given a low-residue diet. Within 10 days the cysts disappeared from his stools and his bowel movements were reduced from 8 to 3 per day. Roentgen examination showed a tubular descending colon and sigmoid, so there is little hope of permanent cure in this case. We feel our patient will suffer from a chronic colitis for the rest of his life.

CASE 4.—C. D. F., a bookkeeper, aged 35, was first seen by us in 1931 when he complained of diarrhea of 5 years' duration. He had 6 to 8 bowel movements a day. An examination of the stool at that time showed the presence of blood. It was otherwise negative. A gastro-intestinal Roentgen ray series was also negative. A diagnosis of colitis was made and the patient was put on a low residue diet and given kaolin (2 gm. t. i. d.) He was relieved and did not return until January, 1933. His symptoms were the same as when first seen. Then proctoscopy revealed typical pin-head ulceration and a proctoscopic smear from the rectal mucosa examined with the warm stage showed many *E. histolytica*. Except for a trip to New England in 1910 the patient had never been outside our metropolitan area but preceding the onset of the present disease he had been engaged in the retailing of vegetables. At that time (1925) he was in the habit of eating raw vegetables from his stand. Particularly was he tempted by Bermuda onions and ate many of them, always uncooked. It is probable that this southern delicacy was the source of his infestation.

It is this case which gives us the most important clue as to the probable epidemiology of amebiasis in this vicinity. The present fad of eating raw vegetables and the increasing quantities of these products being shipped from the South should account for an increase in amebiasis in the next decade.

CASE 5.—C. K., aged 50, an importer of furs, was operated upon by one of us (M. A.) for hemorrhoids, in 1910. The patient had a slight bloody diarrhea after healing of the hemorrhoidectomy wound and, as this continued, Dr. E. J. Ill suggested amebic dysentery. The patient was more or less lost track of until he was again seen in January, 1933. Since 1910 he had had 2 attacks of bloody diarrhea each lasting about 4 weeks. The present 4th attack was of 5 weeks' duration and was accompanied by a perianal abscess. A proctoscopic smear from the rectal mucous membrane was negative, but the stool swarmed with cysts of *E. histolytica*. The source of this patient's infestation no doubt dates back to the Ukraine from which he emigrated to the United States. He said he was accustomed as a child in his fatherland to pick the vegetables from the vines and ground and eat them raw. As he remembered, his father and many of the neighboring farmers suffered from a similar diarrhea.

The symptoms of amebic dysentery are diarrhea and weakness. There is not much pain although there may be occasional colic. The stools are usually liquid, fecal in character and contain blood. The blood may be occult. A proper examination of the stools will show amebæ either in the vegetative or encysted form. With the proctoscope the appearance of the rectum is characteristic. The mucous membrane is studded with small individual ulcers, separated by almost normal or but slightly congested areas.

Noticeable in these cases is that they may continue for years and there may be periods of remission; without treatment the recurrences are apt to be more severe, the bowel becomes more and more involved and some intercurrent infection ends the scene.

The diagnosis is easy if living amebæ are found in the feces or in the material removed proctoscopically from the ulcers. The specimen should be examined as fresh as possible within a few hours after passage, preferable in a warm chamber in order to find living forms. If kept warm for some hours it may be overgrown by colon bacilli. In the cases of chronic diarrhea in which the living amebæ commonly are not found in the stool, a diagnosis is most difficult and several examinations must be made at intervals.

Once the diagnosis is made, the majority of patients are promptly cured by 9 or more intramuscular injections of emetin hydrochlorid ($\frac{1}{2}$ to 1 grain). In the long-standing cases with atrophic changes in the bowel wall and stools showing much pus and other evidence of secondary infection, emetin hydrochlorid is not so effective. Manson-Bahr¹¹ recommends emetin bismuth iodid in these cases in doses of 3 grains per day for 10 or 12 consecutive days. In association with the emetin bismuth iodid, he gives each morning an enema of 2.5 per cent Yatren (iodin-oxyquinolin-sulphonic acid) in warm water (250 cc.). We have used this method in Case 3 with disappearance of cysts from the stool. It was not so successful in Case 5. In association with the treatment we have prescribed the high-caloric, low-residue diet as devised by Barger and Victor¹² in the treatment of chronic colitis. We have felt that placing the large bowel at rest aids in the healing of the lesions. In the treatment of carriers Craig¹³ also mentions the use of emetin bismuth iodid and Yatren. These drugs require that the patient be kept in bed. He found acetarson (Stovarsol) in tablets of 0.25 gm. 3 times a day for 1 week and repeated for a second week after a weeks' rest was effective in banishing the cysts.

Amebiasis is an infestation of the large bowel with *E. histolytica*. Rear Admiral Stitt¹⁴ of our Navy and Manson-Bahr¹¹ both agree that it is a tropical or subtropical disease. And yet we have found these cases in northern New Jersey in individuals who have never been out of the immediate neighborhood in their lives.

To reconcile these opinions and the findings was a problem but we believe we have found the answer. Although the victims of this disorder did not go to the tropics, the tropics came to them.

The infestation is by the mouth and the tropical and subtropical regions, raw fruits and vegetables are the source of the infestation. Sewage and human excrement have long been used as fertilizer and, though forbidden in our own region, there is no doubt of their use elsewhere.

Summary. 1. The endemicity of amebiasis in the states surrounding New Jersey is emphasized.

2. Five cases in New Jersey are reported and the importance of stool examination is stressed as the main factor in diagnosis.

3. Emetin bismuth iodid, emetin, and Yatren are the therapeutic factors of importance.

4. Fresh vegetables from the South are imported to New Jersey throughout the year. Many cases of amebic dysentery in the temperate zone result from eating uncooked contaminated vegetables.

5. A public health warning is uttered to prevent an increase in the cases of this disease.

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ARACHNIDISM: REPORT OF A SERIES OF 29 CASES OF POISONING FROM THE BITE OF THE LATRODECTUS MACTANS.

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THE foreword of one of Emil Bogen's¹ classical papers on arachnidism contains the typical story of a person being most commonly bitten by *Latrodectus mactans*: a young man goes to an outdoor toilet early in the morning, with the resulting inconsequential sting

which he receives on the genitals, followed an hour or more later by the beginning of the dramatic symptoms which mark the climax of poisoning from this insect.

It is a story with which—thanks to the work of Bogen—we are now all more or less familiar; but Bogen^{2,3,4} also calls attention to the fact that we have every reason to believe that *Latrodectus mactans* is not only found in outdoor toilets, but invades habitations, entering beds where human beings sleep, and infests houses, garages, automobiles and other places where its presence becomes a menace. He has reported 380 cases with 17 deaths in 18 states.

In the analysis of the 29 cases which we have collected at this hospital, it will be noted that the majority—16 at least and probably more—received their bites while using an outdoor toilet; but it is the minority in which the bites were not received under these circumstances which particularly attracted our attention. These we desire to discuss in some detail. We cannot help but feel that the idea is being spread and believed at the present time that *Latrodectus mactans* bites are necessarily associated with, first, bites received upon the genitals; and second, with the idea that this accident occurs only where people habitually use outdoor privies. The number of cases seen by us which have been bitten under other circumstances reminds us of the fact that this is not invariably true.

The error which we would be most likely to make—and it has been made—is to treat the case as a surgical emergency. The history, in all probability, has played an important part in leading to this unfortunate conclusion. The following case is presented in detail to call our attention to the fact that in these cases the history, as given by the patient—or any statement given by the patient—may be regarded as misleading or valueless.

Case History. CASE 1 (56390).—A white male, aged 51 years, presented a very interesting problem when first seen by us.

While working in a field, he was stung between the toes, through the interstices of a broken shoe, by a *Latrodectus mactans*. The symptoms came on rather suddenly, and he was seen by a physician before he was sent to the hospital, who gave him $\frac{1}{4}$ gr. of morphin, with very little, if any, effect on the pain from which the man was suffering. It was fortunate we saw this man after an experience extending over several years, which left our minds open to the belief that tremendous terrifying symptoms could be produced by the bite of an insignificant-looking insect. Also some of the staff had heard the history from some members of the family over the telephone. To make this matter absolutely certain, some hours later the *Latrodectus mactans* which had bitten the man was brought to us at the hospital. His suffering was so intense that it was the only thing that could engage his consciousness. Later on we were to find out that he did not remember having been brought to the hospital at all, and only returned to a knowledge of his surroundings when his wife came to visit him at about 7 that evening. He had no knowledge of having engaged in conversation with anybody, and the impression we obtained from him when he first came in was that he would have willingly consented to any procedure, surgical or otherwise, if we would only have given him sufficient morphin

TABLE 1.—DESCRIPTION OF FINDINGS IN 29 CASES OF POISONING FROM THE BITE OF LATRODECTUS MACTANS.

	Case.	Sex.	Color.	Age.	Date.	Temp., °F.	Pulse rate.	Blood pressure.	White blood cells.	Urine.	Urine reten- tion.	Location of bite.	Duration.	Locality.	Abdominal rigidity.
1	21011	M	Wh.	38	7-9-24	97.5	80	?	?	?	No	Penis	24 hrs.	?	None
2	21591	M	Col.	20	8-9-24	97.0	80	?	?	Neg.	No	Genitals	48 hrs.	Privy	None
3	54133	M	Col.	40	6-12-29	98.0	80	?	8,000	Neg.	No	Scrotum	3 days	Privy	Intense
4	47810	M	Col.	53	7-8-28	98.0	100	155/115	9,000	Alb. 3 plus	No	Scrotum	3 days	Privy	Moderate
5	35832	M	Wh.	24	9-22-26	98.6	80	?	?	?	Yes	Penis	2 days	Privy	Moderate
6	35843	M	Col.	23	8-23-26	98.0	90	?	16,000	Alb. 1 plus	No	Penis	4 days	Privy	Intense
7	34754	M	Col.	44	8-5-26	99.0	95	?	8,250	Occ. r.b.c.	No	Penis	24 hrs.	Privy	Moderate?
8	28776	F	Wh.	8	9-7-25	98.0	?	?	19,000	?	No	Hip	24 hrs.	?	Intense
9	59682	M	Col.	23	4-4-30	99.8	85	150/100	6,000	Neg.	No	Penis	3 days	Privy	Intense
10	56390	M	Wh.	51	9-30-29	99.0	52	138/84	10,000	Neg.	No	Foot	2 days	Field	Very intense
11	56751	M	Wh.	16	10-19-29	98.0	80	140/72	15,000	Neg.	No	Finger	3 days	Garage	Intense
12	13309	M	Wh.	19	10-30-29	98.0	72	112/70	?	?	No	Hand	?	Car	Moderate
13	63505	F	Wh.	50	10-17-30	98.6	98	?	11,000	Neg.	No	Vulva	3 days	In bed	Moderate
14	67219	M	Col.	26	5-31-31	98.6	85	150/90	9,000	Neg.	No	Penis	2 days	Privy	Very intense
15	68374	M	Col.	31	8-3-31	98.8	48	145/110	9,000	Neg.	No	Scrotum	2 days	Privy	Intense
16	69339	M	Wh.	45	10-1-31	98.0	80	138/80	12,000	Neg.	Yes	Penis	24 hrs.	Privy	Intense
17	69673	M	Col.	16	10-24-31	99.6	95	?	10,500	Neg.	No	Genitals	24 hrs.	Bowling alley	Moderate
18	70047	F	Wh.	46	11-17-31	99.5	80	?	6,500	Neg.	No	Leg	12 hrs.	Kitchen	Moderate
19	70078	M	Col.	34	11-20-31	98.0	66	150/80	9,750	Neg.	No	Penis	3 days	Privy	Intense
20	70168	M	Wh.	30	11-28-31	98.0	85	138/90	15,000	?	No	Genitals	24 hrs.	In bed	Intense
21	70805	M	Col.	38	1-15-32	97.0	44	135/100	7,000	Neg.	No	Genitals	2 days	Privy	Moderate
22	71071	F	Wh.	30	2-3-32	98.4	80	130/90	26,000	Neg.	Yes	Genitals	3 days	Privy	Moderate
23	71910	F	Wh.	27	4-4-32	98.8	90	146/110	9,500	Alb. 2 plus	No	Leg	24 hrs.	?	Intense
24	72276	M	Col.	28	4-30-32	97.7	80	184/116	7,000	Alb. 2 plus	No	Penis	48 hrs.	Privy	Moderate
25	73320	M	Col.	51	7-11-32	98.0	55	180/112	11,000	Neg.	No	Leg	24 hrs.	In woods	None
26	73775	M	Wh.	17	8-5-32	99.0	78	?	7,000	Pus 2 plus	No	Genitals	3 days	?	Moderate
27	64329	M	Wh.	10	12-12-30	100.0	90	114/75	18,000	Neg.	No	Knee	24 hrs.	In bed	Intense
28	73907	M	Wh.	13	5-13-32	98.0	125	112/88	14,000	Occ. r.b.c.	No	Knee	3 days	Privy	Very intense
29	69176	M	Col.	23	9-21-31	100.0	55	140/80	10,000	Neg.	No	Genitals	24 hrs.	Privy	Moderate

to control his pain and cease to disturb him. All he asked for was death or relief from his agony.

Of all the series, we think this case shows more frankly than any of the others that in some instances at least a history is unobtainable and, when obtained, is worthless.

Two of our cases were bitten while in bed.

CASE 2 (70168).—An adult, awakened with a severe burning sensation in his left groin. At no time could he give us a history of having been bitten by a spider. He arose, went to the barber shop and, while sitting in the barber's chair, the usual symptoms—intense muscular cramping and generalized muscular pain—came on rather suddenly. He was sent to the hospital by an intelligent physician, with a tentative diagnosis of strangulated hernia. The man never suspected or even guessed that he had been bitten by an insect of any description.

CASE 3 (64329).—A fragile white boy, aged 10 years, was also bitten while in bed. He, however, was aware of the fact that something had stung him just above the left knee. The symptoms with him came on rapidly, and he was sent into the hospital, with a tentative diagnosis of a ruptured appendix. Again, fortunately, he was admitted to an atmosphere sympathetic to the story that he had been bitten by a spider and fully prepared to believe the almost unbelievable symptoms from which the boy suffered.

But we could very easily conceive of circumstances under which an accident of this sort could happen, where, without the educational background of the frequency of bites from the *Latrodectus mactans*, the boy's story would be disregarded, particularly in view of the fact that the evidence of the bite at the point at which it was received was negligible. The father, we are quite sure, did not believe the story at all, until he had gone home and, searching through the bed clothing, had found and brought back to the hospital the body of the female *Latrodectus mactans*.

CASE 4 (47810).—A male negro, aged 53 years, was, I believe, the most seriously sick of any of our patients. He developed a rather rapidly progressing and persistent pulmonary edema. The physician who saw him when he was admitted to the hospital suspected that he was seeing the beginning stages of a pneumonia, but subsequent events proved otherwise. This is the only case in which we have seen any evidence of pulmonary edema, and among the few which have shown any shortness of breath.

The case resembles slightly—fortunately not very closely—the case of fatal spider bite which was reported by Beasley.⁵ The recovery, however, was uneventful.

Inability to void has been a fairly common symptom with us, occurring in 3 of the 29 patients. It is rather curious, however, that we have yet to see our first case of eruption following spider bite, although in the West and Southwest this appears to have been a common occurrence following the accident.

Not all of the cases of *Latrodectus mactans* poisoning resemble acute surgical emergencies most closely; one of our cases strongly suggested tetanus. It is the one case also in which we have used

glucose intravenously, with apparently some benefit. We intend to try it on future cases. The history of the case follows:

CASE 5 (73907).—A white male, aged 13 years, was sent into the hospital at 3 A.M. as an acute surgical emergency. There was a boardlike rigidity of the entire abdomen, and he was complaining of severe abdominal pain and of a cramping pain in the legs. This pain seemed to be paroxysmal in character, for he would cry out with pain at rather definite intervals. He insisted on lying on his side with the knees drawn up. The history was obtained mainly from the mother, as the patient had very little to say. He seemed to want to lie perfectly still and not be moved. At 7 o'clock the evening before, the patient had complained of pain in the knees and thighs. At 9 o'clock he was taken suddenly with severe pain in the abdomen, and this pain had continued until the time of admission. Sometime during the forenoon of the day before the patient had had a fall and suffered a rather severe bruise of the left foot, which his mother thought had to do with the symptoms. He had had no similar attacks and there was no history of any digestive disturbances of any kind. After the onset of the abdominal symptoms he was given some soda water, which was vomited, but this was not followed or preceded by any nausea. After questioning, it was found that just prior to the onset of the above symptoms the patient had visited an outside toilet and at the onset was playing in the yard. He did not remember having been bitten by anything or having seen any spider there. On admission the blood pressure was 112/88; pulse, 125; and white blood cells, 13,000.

Examination showed a poorly nourished and very anemic-looking white boy, who appeared acutely ill. The pulse was fast but of good volume; the abdomen was more rigid than we have ever seen; the back muscles were just as rigid; and the back was slightly lordotic. There was no tenderness in the abdomen even on deep pressure. The muscles of the extremities were tense but not rigid, and there was no tendency to spasm even when the patient cried out with pain. There was no abnormality of respiration. It was noted that there was a visible pulsation of the superficial veins of the arms, very much as is seen in an advanced case of arteriosclerosis with hypertension. The superficial and deep reflexes were about normal. The pupils of the eyes were dilated and reacted very sluggishly. He had had no narcotics prior to admission. Morphine, $\frac{1}{2}$ gr., was without any visible effect. Fifty cubic centimeters of 50 per cent glucose was given in the vein, and within 30 minutes the patient was sleeping. The following morning he was comfortable except for some pain in the knees, but the abdomen was as rigid as on admission. The temperature had risen to 99° F. and the pulse rate to 90. On the second day there was some relaxation of the abdominal muscles for the first time, and on the morning of the fourth day he left the hospital with a normal temperature, normal pulse and symptom-free.

Summary. Poisoning from the bite of *Latrodectus mactans* ("black-widow or shoe-button spider") is widely spread throughout the United States.

Inexperienced observers are apt to confuse the symptoms with those produced by an acute intra-abdominal lesion; the symptoms resemble very closely those of a ruptured gastric ulcer.

The mental symptoms lead to further confusion, as the patients are sometimes unable to give a history of having been bitten and are willing to consent to any measure which promises relief.

We have found that a certain proportion of patients are bitten while in bed, which adds still further to the difficulties of a correct diagnosis. It would be advisable to question closely all patients brought into the hospital suffering from marked rigidity of the abdominal muscles, as to the possibility of this accident having happened.

Rigidity of other large muscular masses, particularly those of the thigh and the lumbar region, is an aid in arriving at a correct conclusion.

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DIAGNOSTIC METHODS AND METABOLIC STUDIES IN DISEASE OF THE BILIARY TRACT.

I. DESCRIPTION OF THE ROUTINE EXAMINATION AND DISCUSSION OF NORMAL STANDARDS.*

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AN intensive study of diseases of the liver and biliary tract has been made possible through the organization of a specialized Gall Bladder Clinic, with a combined medical and surgical staff collaborating with bacteriologic, biochemical, and roentgenologic laboratories. All patients admitted to this clinic have been studied on a uniform schedule including history, physical examination, cholecystogram, drainage of the biliary tract with microscopic, chemical and bacteriologic analysis of the bile fractions, chemical analysis of the urine and special tests of liver function. The improvement resultant upon treatment has been evaluated by repetition of the initial diagnostic procedures. To date, 500 patients have been studied and 3000 drainages performed according to the routine schedule. Data accumulated by the chemical analysis of the blood and bile,

* This work has been aided by a grant from the Oliver Rea Fund.

obtained from these patients under uniform conditions, interpreted in the light of all clinical and other laboratory findings possess a two-fold interest both for the clinician and for the laboratory investigator. They afford (a) abundant material for the evaluation of such analyses as aids in diagnosis of organic and functional disturbances of the liver, gall bladder and bile ducts and often aid in a differential diagnosis of the two, and (b) they may serve as contributions to a better understanding of the relations of these organs to metabolism.

Such a study is needed, as any method of diagnosis may be misleading at times. The history of biliary tract disease is usually indefinite, except for the relatively uncommon symptoms of jaundice and typical colic. Physical examination is of limited value; tenderness in the right upper quadrant of the abdomen or the presence of a palpable liver or gall bladder does not necessarily lead to a correct diagnosis. Roentgenographic study cannot always demonstrate the presence of stones or explain the physiologic or pathologic changes which prevent visualization of the gall bladder. The importance of these uncertainties cannot be overestimated because of their bearing upon decisions as to the advisability of operation.

Our object here is to present our results, particularly in regard to conditions of the blood and bile in a group of 10 control subjects and 30 patients having apparently normal biliary tracts. The controls were 8 male and 2 female members of the clinic and laboratory staff, from 21 to 47 years of age, who, having had no history or clinical signs of biliary tract disease, volunteered to go through the diagnostic routine of the clinic. The 30 normals were patients, 10 males and 20 females from 24 to 63 years of age, who on admission to the clinic complained of mild types of gastro-intestinal symptoms but in whom disease of the biliary tract was excluded on the basis of all diagnostic criteria.

Methods and Results.—Cholecystograms were made under the direction of Dr. William H. Meyer, in all cases presented. Oral administration of the dye has been used in practically all instances, and this procedure is usually repeated if the result of the first examination is unsatisfactory. With gastro-intestinal disturbances such as vomiting or diarrhea following ingestion of the dye, or in those cases in which there are no visualizations of the gall bladder, the intravenous method of dye administration is used. Cholecystograms of the 10 control individuals revealed normal "visualization" and normal rates of evacuation of the gall bladder in all cases. Normal "visualization" of the gall bladder was observed in all of the 30 presumably normal cases. Four of these subjects exhibited a slight delay in emptying of the gall bladder in response to a meal rich in fats, which was interpreted as being probably of no significance.

For biliary tract drainage, the patient reports at 8.30 A.M. without breakfast. The general method of procedure is that described by Lyon.¹ The duodenal tubes usually used are those of the metal-tip type: the Rehfuß, Lyon, or one designed by one of the authors² which has the advantage in our experience of being more quickly introduced into the duodenum and more easily retained there. Duodenal intubation may be done with the

patient in the Fowler position or upright, with or without fluoroscopic guidance as described by Morgenstern.³ The Levin catheter tip tube has also been used. Following a gastric lavage, the tube is introduced into the duodenum, according to the method described elsewhere.⁴ The arrival of the tip at this point is indicated by the drainage of clear bile, the usual absence of free hydrochloric acid (as shown by Congo paper), or by fluoroscopic examination.

The first bile obtained is generally golden-yellow, this is labelled the D_1 specimen, as shown in Table 4. An ounce of warm 16 per cent magnesium sulphate is then injected and allowed to remain 2 minutes, the bile being obtained by syphonage. Two similar injections of 25 per cent magnesium sulphate are then used, these specimens are labelled M_1 , M_2 , and M_3 . If no concentrated brown or olive-green bile is obtained in this way, an ounce of warm olive oil is instilled and allowed to remain in the duodenum 10 minutes, the resulting specimen is labelled O_1 . Following the drainage of dark bile there is usually light yellow or lemon-yellow bile; this is called the D_2 specimen.

Concentrated bile was obtained in all cases of both the control and normal groups. The sediment of all bile specimens was procured by means of a pipette and examined microscopically, especially for crystals of cholesterol, calcium bilirubinate pigment, bile-stained pus cells, and columnar epithelial cells. Examination of the sediment for pathologic elements was negative in all specimens of the control subjects. The 30 normal cases were also negative microscopically except for one in whom occasional cholesterol crystals were found.

Results of the chemical analysis of the blood and bile fractions for the 40 subjects are presented in the accompanying tables. These data have been assembled for the controls and normals under conditions analogous to those for pathologic states of the biliary tract (to be presented later) and represent the normal standards and the range of variations to be expected under physiologic conditions.

Total cholesterol of whole, oxalated blood was determined by the Sackett modification of the Bloor method.⁵ The control group has an average figure of 189 mg. and the normals 200 mg. per 100 milliliter of blood. Bruger and Somach⁶ in a recent report upon the diurnal, physiologic variations in the cholesterol content of whole blood and of plasma of subjects in the absorptive and in the fasting state, have shown that deviations from the mean are least during the morning hours, between 9 A.M. and 1 P.M. Sackett's method has been adopted for analysis of blood and bile for cholesterol.²³ Since the specimens of blood reported in our tables were taken between 9 A.M. and 10 A.M., during a fasting state, the figures are comparable with those reported by Bruger and Somach. It is significant to note that the standard deviations for both groups, ± 2.8 and ± 3.4 per cent, are less than the average standard deviation of ± 3.9 per cent reported by Bruger and Somach for this period of the day.

In the determination of cholesterol ester, free cholesterol was separated from the bound cholesterol by precipitation with digitonin. Similar average ratios of cholesterol esters: total cholesterol were calculated for both groups, between extremes of 0.30 and 0.69. Bloor and Knudson⁷ have stated that this ratio may vary from 0.40 to 0.70.

The occurrence of bile acids in normal blood and the variations from the average normal concentration in pathologic states have been the subject of numerous reports expressing conflicting opinions within recent years. With a modification of Szilard's method, Katayama⁸ found an average of 7 mg. of bile acids, as glycocholic

acid, per 100 milliliters of blood. Aldrich and Bledsoe,⁹ using a quantitative Pettenkofer test, report values in normal blood equivalent to from 3 to 6 mg. of glycocholic acid for each 100 milliliters of blood. Walker¹⁰ believes that the substance giving Pettenkofer reaction is not bile acid but probably cholesterol oleate. Perlzweig and Barron¹¹ found no bile acids in normal blood but obtained quantitative recoveries of added bile acids. A preliminary report by Tashiro¹² presents high figures for bile acids in the bloods of jaundiced patients but no values for normal blood. All methods employed by various analysts for bile acids in blood are based upon non-specific color reactions or precipitations, hence there is doubt about the chemical identity of the reacting substances reported as bile acids. While we await the isolation of bile acids from blood and their identification, in the interpretation of analytical results it is necessary to bear in mind that the material reacting in the analytical procedures is assumed to be bile acids only because its response to reagents is similar to that of pure solutions of the bile salts, and the analytical methods yield good recoveries of added bile salts.

The modification of the Szilard method, described by Katayama,⁸ was adopted for determination of bile acids in blood and bile. In the series of 10 control subjects the bile acids calculated as glycocholic acid gave an average figure of 7.5 mg., with extremes of 19 and 3 mg., per 100 milliliters. For the 30 normal cases the average figure for bile acids was 13.6 with extremes of 22 and 3 mg. per 100 milliliters. For both series the icterus indices¹³ of the serum were within the normal range, varying between extremes of 4 and 8. In the chemical analyses of blood the following procedures were used: Folin and Wu's method for sugar,²⁰ the aëration method described by Myers for urea nitrogen²¹ and the Clark-Collip modification of the Kramer-Tisdall method for calcium.²² For urea nitrogen of the blood, a wide range of variation was observed for both series. The average figures, however, show close agreement. The blood sugar levels for all of the cases were well within the normal limits. Also the figures for the blood serum calcium fell within the normal range. In the routine chemical analysis of the blood, determinations of the sugar and urea nitrogen were included as indices of disturbances of carbohydrate metabolism and renal function.

The results of bile analysis indicate that the average deviations found are not greater, generally speaking, than would be allowed for the experimental error in the method used. The D₁ bile is the clear golden-yellow bile obtained before stimulation, as previously described. A postoperative study of bile obtained by the duodenal tube simultaneously with bile obtained by means of a drainage tube in the common duct has indicated that the two specimens were similar in composition and that the factor of dilution is not of practical importance. The concentrated bile (M or O specimens) is the dark, thick, brown or olive-green bile usually obtained after repeated

stimulation; this is the "B" bile as described by Lyon. This study differs from that of McClure ^{14,15} in the differentiation of the various types of bile. We believe that this is important as it is always necessary to differentiate between changes in the composition of the bile which have been produced on the one hand by changes in the secretory activity of the liver and on the other hand by the contraction of the gall bladder.

TABLE 1.—RESULTS OF ROENTGENOLOGIC STUDY AND BILIARY TRACT DRAINAGE. IN 10 CONTROL SUBJECTS.

Cholecystograms taken	10
Normal "visualization"—normal emptying	10
Biliary tract drainages performed	10
Concentrated bile obtained	10
Negative microscopic examination of biliary sediment, all specimens	10

IN 30 NORMAL CASES.

Cholecystograms taken	30
Normal "visualization"—normal emptying	26
Normal "visualization"—delayed emptying	4
Biliary tract drainages performed*	30
Concentrated bile obtained	30
Negative microscopic examination of biliary sediment, all specimens	29
Cholesterol crystals, occasional	1

* In all doubtful cases drainages are repeated.

TABLE 2.—CHEMICAL ANALYSIS OF BLOOD OF 10 CONTROL SUBJECTS.

Constituent.	Maximum. (All values in mg. per 100 ml. blood.)	Minimum.	Average.	Average deviations.
Total cholesterol	200	175	189	±8
Cholesterol esters	110	67	90	±10
Cholesterol ester	0.55	0.34	0.46	±0.1
Total cholesterol				
Bile acids as glycocholic	19	3	7.5	±5.5
Urea N	14	7	11	±2
Sugar	93	70	83	±5
Calcium of serum	11	10	10.4	±0.3
Icterus index of serum	8	4	6	±1.0

Inspection of the bile fractions obtained by drainage in the entire series of 40 cases showed concentrated bile to be present in all cases. This finding is in agreement with the cholecystograms, assuming concentrating power of the gall bladder to be indicated by the intensity of its visualization.

In the chemical analysis of the duodenal (D₁) bile, cholesterol was present in sufficient amounts to be determined quantitatively in only 7 cases. Cholesterol was found in all specimens of concentrated bile, the concentration varying from a trace to 361 mg. per 100 milliliters of bile. The cholesterol content of the concentrated bile is in practically all cases distinctly higher than that of the duodenal specimens. The cholesterol content of the D₂ bile obtained after the concentrated specimen usually approximates that of the D₁ specimen.

TABLE 3.—CHEMICAL ANALYSIS OF BLOOD OF 30 NORMAL SUBJECTS.

Constituent.	Number of analyses.	Maximum. (Mg. per 100 ml.)	Minimum.	Average.	Average deviations.
Total cholesterol	30	294	153	200	±20
Cholesterol esters	23	147	56	95	±15
Cholesterol esters	20	0.69	0.30	0.47	±0.19
Total cholesterol	30	22	3	13.6	±3.4
Bile acids as glycocholic	30	16	4	9	±2
Urea N	29	97	64	83	±9
Sugar	9	11	9	9.8	±0.4
Calcium of serum	30	8	4	6	±1.0

Bile acids were found in all specimens of D₁ bile, the average amounts for the two groups of cases being 39 mg. and 28 mg. per 100 milliliters of bile. The concentrated bile contained from 2 to 13 times the bile acid concentration of the duodenal bile.

TABLE 4.—ANALYSIS OF BILE FRACTIONS OF 10 CONTROL SUBJECTS.

Constituent.	Bile fraction.	Maximum. (Mg. per 100 ml.)	Minimum.	Average.	Average deviations.
Cholesterol	D ₁	Trace	Trace	Trace	0
	Conc.	92	Trace	51	±35
	D ₂	49	Trace	9	±15
	D ₁	63	18	39	±9
Bile acids as glycocholic	Conc.	311	109	228	±42
	D ₂	108	Trace	30	±25
	Conc.	13	2.8	6.5	±1.9
	D ₁				

The absorption of fluid and the consequent concentration of the bile by the gall bladder is generally conceded. At the beginning of our investigation the ratios of the concentration of the duodenal (D₁) and concentrated specimens were studied in an effort to obtain an index of gall bladder function. There are difficulties in the use of such an index because it is recognized that even though the concentrated bile arises in the gall bladder it probably is mixed with an indeterminate amount of bile from the liver in the course of the drainage. As a result the concentration ratios are less than those which we obtain by analysis of the bile removed from the gall bladder at operation. Nevertheless this study has been of value. Of particular interest is the discrepancy between the concentration ratios of cholesterol and bile acids. The average concentration ratio of cholesterol is approximately 50 and the average concentration ratio of the bile acids is about 5. These differences can be explained either as due to the absorption of bile acids by the gall bladder, as suggested by Rosenthal and Licht,¹⁶ or to the secretion of the cholesterol by the latter viscus as suggested by Elman and Taussig¹⁷ and Elman and Graham.¹⁸ On the other hand Andrews and his associates state that there is no differential absorption of cholesterol and bile salts by the gall bladder wall. Unfortunately

these data deal only with the relative concentrations of the different substances concerned and so will not permit a decision between these theories.

TABLE 5.—ANALYSIS OF BILE FRACTIONS OF 30 NORMAL SUBJECTS.

Constituent.	Bile fraction.	Num-ber of analyses.	Maxi-mum. (Mg. per 100 ml.)	Mini-mum.	Average.	Average deviations.
Cholesterol	D ₁	19	41	Trace	7	±11
	Conc.	21	364	Trace	80	±60
	D ₂	8	104	Trace	17	±25
	D ₁	29	72	15	28	±7
	Conc.	30	391	45	367	±66
Bile acids as glycocholic .	D ₂	9	68	37	45	±7
	Conc.					
	D ₁	27	12	1.9	4.9	±1.1

The concentrating power of the gall bladder as measured by the intensity of the cholecystographic shadow was found to correspond more closely to the concentration of the bile acids in the concentrated specimen than it did to the concentration of cholesterol in the same specimen.

Bacteriologic studies of the various types of bile obtained on sterile drainage have been made under the direction of Dr. Adele Sheplar. A broth culture is first made of the set to determine its sterility. Cultures and plates are then made of each type of bile. In many patients we have obtained sterile cultures consistently, or a single organism repeatedly. The results of this study are being checked in all cases coming to operation, when a culture is made of the gall bladder bile, the gall bladder wall, the cystic duct node, and of stones if present. A report will be made at a later date concerning these findings.

Summary. A routine of study for diseases of the biliary tract is presented with findings in 10 control individuals and 30 patients in whom a complete investigation showed no evidence of biliary tract disease.

This investigation has included: History, physical examination, cholecystogram, duodenal drainage, inspection of bile specimens, microscopic examination of biliary sediments, chemical analyses of blood and bile, icterus index determination, van den Bergh reactions and the bacteriologic study of bile.

The findings in both series of patients are presented as standards for comparison with findings in cases of suspected gall bladder or liver disease.

Results indicate that with a normally functioning biliary tract these tests should show:

(a) A satisfactory "visualization" of the gall bladder on roentgenographic study.

(b) The presence of 30 to 60 milliliters of concentrated bile during non-surgical biliary tract drainage.

(c) The absence of pathologic elements on microscopic examination of the biliary sediment in all specimens.

(d) Little or no cholesterol in the D₁ and D₂ bile.

(e) Bile acids of the concentrated bile fraction 4 to 7 times greater than that of the duodenal bile.

(f) The absence of pathogenic organisms which occur repeatedly in bile obtained by sterile duodenal drainages.

(g) A blood serum icterus index reading of 4 to 8, a negative direct van den Bergh reaction.

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GALACTOSE TOLERANCE AS A MEASURE OF LIVER FUNCTION.

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GALACTOSE tolerance was first proposed as a liver function test by Bauer¹ in 1906. As extensive reviews of the literature on this test have been published, reference to the earlier work upon this subject need not be made. In this test, as it is most widely used,

40 gm. of galactose is given by mouth and the galactose excreted in the urine during a 5-hour period following ingestion is determined. If the urinary galactose for the 5-hour period exceeds 3 gm., it is considered evidence of hepatic insufficiency. Recently studies of the total blood-sugar concentration and the degree of galactosuria following galactose ingestion have been made by Machold,² Bode,³ and Pollak.⁴ The determination of the total blood sugar following galactose administration does not give specific information regarding the amount of galactose in the blood, hence we thought it of interest to study the blood galactose concentration following galactose ingestion in normal subjects and in patients with representative types of liver damage.

In beginning our work it seemed important to establish a uniform dosage of galactose. The arbitrary use of a fixed dosage of galactose for all patients, regardless of size, did not seem satisfactory, because of the differences in the amounts of intestinal absorptive surface and of liver and muscle tissue in subjects of varying sizes. We, therefore, adopted the use of 1 gm. of galactose per kilogram of body weight as a dosage which we believe gives more comparable results than the arbitrarily established 20- to 40-gm. amounts that have been used by different workers.

The procedure used by us for the studies of this report is as follows: The test is carried out under fasting conditions, usually in the morning. A control sample of blood is obtained and galactose dissolved in a convenient quantity of water is given by mouth. Blood samples are collected $\frac{1}{2}$ hour, 1 hour and 2 hours after ingestion, and a single urine sample is collected at the end of the 2-hour period. The galactose content of the blood and urine samples is then determined. The blood galactose is estimated by the method developed by ourselves.⁵ The urinary galactose is determined by titrating against Benedict's quantitative copper solution, 1 cc. of which is reduced by 0.0025 gm. of galactose. In order to obtain a study of the relation between the total sugar of the blood and the blood galactose following galactose ingestion, we also determine the total blood sugar by Benedict's method.⁶

A study of the galactose tolerance of 10 normal subjects by the procedure described above was recently made by us.⁵ In Table 1 a part of our data is reproduced, to show the relation of the concentration of galactose in the blood to the amount of galactose excreted in the urine. It has been generally claimed that the kidneys do not maintain a threshold for galactose excretion and hence the part played by the kidneys has no significance in the interpretation of the degree of galactosuria obtained following galactose ingestion. The evidence obtained by us does not agree with this conception. The data of Table 1 show that the amount of galactose in the urine does not parallel the levels of galactose in the blood. This evidence indicates that the kidneys maintain a threshold for galactose excre-

tion which varies considerably in normal subjects. This is well illustrated by subjects H. D. and J. R., who received essentially the same dose of galactose. With subject H. D., the highest blood galactose obtained was 80 mg. per 100 cc. and the urinary galactose was 0.91 gm. With subject J. R., the highest blood galactose was 63 mg. per 100 cc., and the urinary excretion was 2.48 gm. Subjects G. R. and A. S. present a like contrast. With subject G. R. we obtained the highest blood galactose of our series, 138 mg. per 100 cc., and the urinary galactose of this subject was 1.75 gm. With subject A. S. we obtained the next to lowest blood galactose in our series of 10 subjects, which was 39 mg. per 100 cc., and the urinary galactose was 2.25 gm. Similarly other contrasts may be drawn from this table. These data show the existence of a galactose kidney threshold which varies in different subjects, just as the kidney threshold for glucose excretion varies.

TABLE 1.—GALACTOSE TOLERANCE OF NORMAL SUBJECTS.

(From the Data of Roe and Schwartzman, *J. Biol. Chem.*, 1932, 96, 717.)

Subject.	Sex.	Galac- tose in- gested (gm.).	Galactose in 2-hour urine sample (gm.).	Blood galactose (mg. per 100 cc.).			
				Control (saccha- roid).	$\frac{1}{2}$ hr.	1 hr.	2 hrs.
H. D.	F.	74	0.91	7	28	80	34
C. S.	F.	44	0.92	7	90	109	34
A. M.	M.	66	1.00	8	29	37	32
R. E.	M.	64	1.00	9	32	67	30
F. B.	F.	60	1.35	10	53	100	29
G. R.	M.	70	1.75	10	67	138	101
E. B.	F.	58	2.20	9	53	89	118
A. S.	M.	61	2.25	7	35	39	36
J. R.	M.	75	2.48	9	56	63	33
G. Y.	F.	59	2.78	11	80	120	106

From our studies with normal subjects we came to the conclusion that better evidence is obtainable concerning the functioning of the liver by determining the circulating level of galactose in the blood than by determining the urinary galactose excretion, although the estimation of both of these is of interest.

The results of our studies of 17 cases of liver disease are summarized in Table 2, and are shown graphically by the curves of Fig. 1. In the cases of cirrhosis, metastatic carcinoma, passive congestion due to heart failure, and toxic or chronic degenerative hepatitis, the blood galactose curves and the urinary galactose excretion are well within the limits obtained with 10 normal subjects. These cases do not show any evidence of reduced galactose tolerance and they indicate that the galactose tolerance liver-function test may not be expected to give evidence of diagnostic value in the types of liver disease of which they are representative. This is especially indicated by C. S., a case of severe portal cirrhosis with ascites. In this case there was marked bilirubin retention and the bromsulphalein test showed 90 per cent retention of dye in the 30-

TABLE 2.—GALACTOSE TOLERANCE OF CASES WITH LIVER DISEASE.

Subject.	Sex.	Galac- tose in- gested, gm.	Blood sugar, mg. per 100 cc.							Galactose in 2-hr. urine sample, gm.	Diagnosis.	Method of diagnosis.	Other data.*
			Galactose.			Total sugar as glucose.							
			Con- trol.	1 hr.	2 hrs.	Con- trol.	1 hr.	2 hrs.					
C. S.	M.	90	..	38	41	29	...	154	148	128	Cirr. with ascites	Aut.	J.; bili., 21 mg. per 100 cc.; I. I., 150; Bs., 90% retention.
J. J.	M.	65	8	31	63	28	70	92	129	105	Atrophic cirrh.	Clin.	
M. S.	F.	73	5	..	45	47	80	...	110	98	Banti's dis.	Clin.	
R. A.	M.	48	5	17	12	15	73	73	74	88	Metast. carc. liver	Biop.	
C. G.	M.	50	10	20	28	31	81	93	103	109	Metast. carc. liver	Biop.	
S. G.	M.	48	5	21	30	33	52	63	88	88	Metast. carc. liver	Clin.	
J. W.	M.	60	9	32	96	47	62	79	139	97	Cong. ht. failure	Clin.	
F. B.	F.	70	8	23	29	28	83	110	101	112	Cong. ht. failure	Clin.	J.; bili., 7.1 mg. per 100 cc.
E. T.	M.	75	11	32	61	69	80	96	109	103	Cong. ht. failure	Clin.	
P. H.	F.	50	7	22	93	115	70	85	123	152	Tox. degen. hepatitis	Clin.	Bs., 25% retention; bili. normal (6 days after galactose test).
D. L.	F.	50	4	17	30	56	68	84	93	109	Chr. degen. hepatitis	Clin.	Bili., 0.8 mg. per 100 cc.; I. I., 50; Bs., neg.
W. P.	M.	63	9	38	81	125	85	112	130	167	Chr. degen. hepatitis	Clin.	Bili., 1 mg. per 100 cc.
M. R.	F.	65	10	10	16	13	111	95	105	113	Cholelith.	Oper.	J.; bili., 20 mg. per 100 cc.; I. I., 160.
A. M.	M.	65	10	98	143	21	82	135	167	94	Ac. catarr. J.	Clin.	J.; bili., 6.7 mg. per 100 cc.; I. I., 90.
A. M.	F.	50	8	51	125	230	74	102	150	222	Ac. catarr. J.	Clin.	J.; bili., 15 mg. per 100 cc.; I. I., 83; Bs., 25%.
A. B.	M.	50	4	68	123	39	67	105	156	94	Ac. catarr. J.	Clin.	J.; bili., 11.2 mg. per 100 cc.; I. I., 150.
B. C.	F.	73	9	41	122	143	79	111	159	197	Ac. catarr. J.	Clin.	J.; bile in urine.
											Ac. catarr. J.	Clin.	J.; bili., 10.3 mg. per 100 cc.; I. I., 100.

* J. = jaundice; bili. = bilirubin; I. I. = icterus index; Bs. = bromsulphalein.

minute sample, yet the blood-galactose curve was that of a low normal. In the other cases of chronic liver disease there was shown a similar lack of sensitivity of the galactose tolerance test as compared with other tests for liver damage.

In 4 cases of catarrhal jaundice the blood galactose reached a level which was either around that of our highest normal case or was considerably above that of our normal subjects. In catarrhal jaundice then one may expect to find evidence of reduced galactose tolerance and the galactose tolerance liver-function test here may be of diagnostic value. In contrast with the high values obtained in catarrhal jaundice, the low blood-galactose curve and reduced urinary galactose excretion obtained with M. R., a case of cholelithiasis with

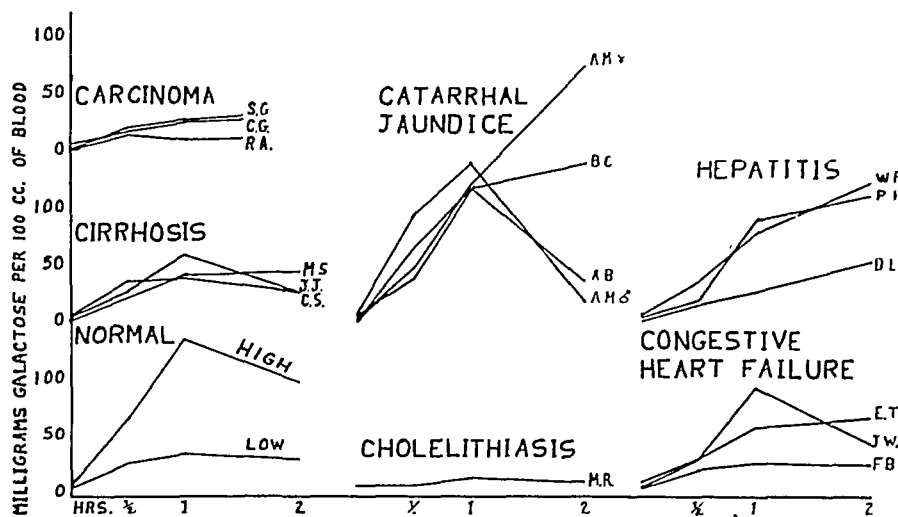


FIG. 1.—Blood-galactose curves of cases with liver disease. (From the data of Table 2.)

marked jaundice, show that the galactose tolerance test may be of considerable value in the differential diagnosis of obstructive jaundices of infectious and non-infectious origins. These conclusions are in agreement with the report of Shay, Schloss and Rodis,⁷ who obtained their evidence by studies of the urinary galactose excretion only.

In general the data obtained by us with 17 cases of liver disease indicate that in chronic liver disease one may not expect to obtain evidence of functional disturbance of the liver by the galactose tolerance test unless very severe and widespread liver damage exists. This is apparently because in chronic liver disease the regeneration of functional liver tissue is usually rapid enough or the margin of safety great enough to provide for the carbohydrate metabolism of this organ. The test may be of value, however, in acute liver disease. In cases of acute liver lesions, such as catarrhal jaundice, the onset of the disturbance is rapid; consequently the

capacity of the liver to metabolize carbohydrate is reduced and evidence of this disturbance may be obtained by the galactose tolerance liver-function test.

The total blood sugar following galactose ingestion was determined in order to study the relation between the total blood sugar and the blood galactose. In general the total blood-sugar curves parallel the blood-galactose curves in the cases of liver disease which we studied and no additional information was obtained by estimating the total blood sugar. From our experience we recommend a procedure in which only the blood galactose is estimated, as this is as simple as that of the total blood-sugar determination, and the blood-galactose concentration is a more specific indication of the capacity of the liver to metabolize galactose. An additional advantage of determining the blood galactose rather than the total blood sugar, as others have recommended, is that the collection of a control sample of blood previous to galactose ingestion is unnecessary, thereby reducing the number of venipunctures. As the dosage used by us differs from that used by other workers, we are unable to make comparisons of our total blood-sugar findings following galactose ingestion with any of the reports in the literature.

In our studies the highest blood-galactose concentration usually came 1 hour after ingestion of galactose. The peak of the galactose curve never occurred at the $\frac{1}{2}$ -hour interval. It is therefore useless to estimate the galactose in a sample of blood collected $\frac{1}{2}$ hour after ingestion. Occasionally the greatest elevation of the blood galactose occurred in the sample collected 2 hours after ingestion. From these observations we recommend that the blood collection procedure followed in this paper be modified and that for this test samples of blood be taken at 1-hour intervals for 3 hours following galactose ingestion. The collection of a control sample of blood is obviously unnecessary, as there is no galactose in fasting blood.

From our studies the following interpretations are suggested regarding the proposed galactose tolerance liver-function test, in which 1 gm. of galactose per kilo of body weight is given by mouth under fasting conditions:

1. A galactosemia in excess of 150 mg. per 100 cc. of blood following the ingestion of galactose, in the presence of supporting clinical evidence, is pathognomonic of liver disease.

2. Blood-galactose values between 125 and 150 mg. per 100 cc. of blood at the peak of the galactosemia must be considered as borderline values. In the presence of supporting clinical evidence such values may be taken as evidence of reduced liver function. Normal subjects, however, may be expected occasionally to show blood-galactose values within, or possibly slightly above, this range following the ingestion of the designated dosage of galactose.

3. Blood-galactose values below 125 mg. per 100 cc. of blood must be considered as a normal response following the ingestion

of the proposed dosage of galactose, but should not be regarded as eliminating liver disease.

Summary. 1. A study of the galactose tolerance of normal subjects and patients with representative types of liver disease has been made by determining the blood and urinary galactose concentration following the ingestion of galactose by mouth. Data are presented showing that following galactose ingestion, the blood-galactose concentration is a better indication of liver function than the urinary galactose excretion since it is not influenced to the same extent by a variable renal threshold.

2. Blood-galactose concentrations similar to those of normal subjects were obtained in cases of cirrhosis, metastatic carcinoma, congestive heart failure, toxic and chronic degenerative hepatitis. The urinary galactose excretion in these cases was essentially the same as observed in normal subjects. These studies indicate that the galactose tolerance liver function test may not be expected to give evidence of diagnostic value in chronic liver disease.

3. Blood-galactose values higher than normal were observed in cases of acute catarrhal jaundice. A normal response was obtained in a case of cholelithiasis with marked jaundice. These findings indicate that the galactose tolerance liver function test may be of value in the differential diagnosis of jaundices of infectious and non-infectious origins.

4. Based upon these studies a new technique for the galactose tolerance liver-function test is proposed. In this test 1 gm. of galactose per kilo of body weight is given by mouth under fasting conditions and the galactose content of samples of blood collected at hourly intervals for 3 hours following ingestion is determined. Data are presented for the interpretation of findings obtained by this technique.

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REVIEWS.

A DICTIONARY OF GREEK AND LATIN COMBINING FORMS USED IN ZOOLOGICAL NAMES. By EDMUND C. JAEGER, Head of the Department of Zoölogy, Riverside Junior College, Riverside, Calif. Pp. 157. Second edition. Springfield, Ill.: Charles C Thomas, 1931. Price, \$1.50.

THE amusement that the layman often gets out of apparently cumbersome scientific names should cause no embarrassment to the scientist who realizes that the single word may carry a wealth of meaning within its polysyllables. With the regrettable decadence of knowledge of Latin and Greek, however, this advantage is being more and more lost, and a dictionary such as this becomes correspondingly more and more valuable. Though the more than 2000 words here included contain much of medical interest, we are churlish enough to wish that it had been further extended in scope and content. This remark is intended to serve also as a compliment to the producers on the success of their undertaking. E. K.

SEX AND INTERNAL SECRETIONS. By various contributors. Edited by EDGAR ALLEN, University of Missouri. With a Foreword by ROBERT M. YERKES, Yale University. Pp. 951; illustrated. Baltimore, Md.: The Williams & Wilkins Company, 1932. Price, \$10.00.

THIS volume is really a series of 19 reviews, broadly covering the question of sex and endocrines, by 21 American authors selected for their competence and authority. The subjects presented include: genetics, and the interrelationship of genic and endocrine factors; embryologic foundations of sex in vertebrates; sex deviations and inversions; metabolism of sex; the control of plumage in birds; histologic changes in the pituitary; ovulation, and the transport of ova and sperm; the physiology of the mammary gland; the biology and chemistry of the secretions of the ovary, testis and pituitary; the biologically active substances of pregnancy urine, including a discussion of pregnancy tests; and, finally, endocrine disorders in man. It is probably true that no one man could have written this volume, so broad is its scope; likewise is it highly probable that no one man could review this entire work adequately. For this reason alone this volume should prove to be of great value to all biologists interested in sex in its broadest sense. It is doubtful if even the most learned student in the field could read this book without learning much of value to him, much that he would like to know . . . and did not.

In the words of the editor, it was the purpose of this coöperative effort "to survey the most important recent researches in problems of sex, especially those concerned with internal secretions, in order that the concepts already established by experimental evidence may be clearly stated and made easily available." It is readily apparent that this purpose has been handsomely fulfilled. Each of the 19 chapters is singularly well written, the subject matter being clearly and tersely stated. The chapters dealing with material familiar to the Reviewer adequately cover the field, the one

exception being the chapter on the corpus luteum. Here the discussion is limited to the work with corpus luteum extracts, and this is unfortunate in so far as some of the most important and thought-provoking work on the corpus luteum has been omitted or given scant notice. Through skillful editing duplication of material by the several authors has been avoided, and helpful cross-references guide the reader to a fuller discussion of any point cited by more than one author.

One adverse criticism concerns the limitation of space and emphasis devoted to controversial matter, and to those stubborn facts which do not fit prettily into any hypothesis that can at present be formed from the bulk of the material at hand. More emphasis here would have produced a volume much more challenging to thought and provocative to further research, though we recognize that it might have expanded the material to a mass too unwieldy for one volume. Because it is one volume, and because it contains between its covers so much of our present knowledge of sex and endocrines, herein lies its chief value. With the full bibliographies at the end of each chapter, and the excellent author and subject indices, it should be an indispensable reference work. For the average physician this book would probably not be a prudent investment; it contains much that would not interest him and too much of that which would interest him. It is the gynecologist and the obstetrician who will find profit in this volume. Those who seek to keep abreast of the times will find it a comforting guide to the important developments which in this field have come so rapidly as to bewilder even the investigators.

M. F.

CASE STUDIES IN THE PSYCHOPATHOLOGY OF CRIME. By BEN KARPMAN, M.D., Psychotherapist, St. Elizabeth's Hospital; Professor of Psychiatry, Howard University, Washington, D. C. Pp. 1026; 14 charts. Washington, D. C.: Mimeoform Press, 1933. Price, \$12.00.

In the 5 case reports constituting this volume, the author has endeavored to embody all available information bearing upon the psychogenetic elements conducive to criminality. Each obvious physical ailment was given appropriate attention, after which treatment was psychoanalytic.

One must differ from the writer in saying "criminals are sick people." A bad man is not necessarily a sick man. Often he appears just vicious—showing atavism—reversion to an earlier type. The volume is unique and its value would be enhanced by condensation and perhaps by such phraseology as would relieve it of seeming obscenity, thereby overcoming those legal restrictions necessarily placed upon the distribution of such literature. This has been achieved by Havelock Ellis and other writers. Few readers know the meaning of "punk," "wolf" and "stir-wise," hence a brief glossary giving the prison vernacular would be helpful.

N. Y.

PRACTICAL HEMATOLOGICAL DIAGNOSIS. By O. H. PERRY PEPPER, M.D., Professor of Clinical Medicine, University of Pennsylvania; Assistant Chief of the Medical Clinic, Hospital of the University of Pennsylvania, and DAVID L. FARLEY, M.D., Physician to the Pennsylvania Hospital, Philadelphia, and to the Cooper Hospital, Camden, N. J.; Associate in Medicine at the University of Pennsylvania. Pp. 582; 3 plates of colored illustrations. Philadelphia: W. B. Saunders Company, 1933. Price, \$6.00.

THE dearth of good works on hematology in English is largely filled by this welcome work. Still more, the authors' aim of "presenting the prac-

tical aspects of clinical hematology in simple terms" has been so well achieved that we now have something different than just another good text-book. The efficiency of composition and exceeding clarity of exposition—not usually strong points in American text-books—stand out to such a degree that the book might well be studied to advantage by those contemplating text-book production. Part I, comprising almost half the book, deals with the blood cells, methods of study and significance of results. Part II, the shortest section, deals with specific disorders of the hemolytopoietic system. Part III (159 pages), presents in concise but adequate form the hematologic findings of some 400 diseases not primarily of the blood. This feature, which is unique, as far as the Reviewer is aware, should be of especial use to the general practitioner. Where the general standard is so high, we can well afford to forebear from mentioning the occasional items that might have been improved. We predict a useful and honorable career for this very practical addition to hematologic literature. E. K.

CHAPTERS IN AMERICAN OBSTETRICS. By HERBERT THOMS, M.D., Associate Professor of Obstetrics and Gynecology, Yale University School of Medicine. Pp. 90; 10 plate illustrations. Springfield, Ill.: Charles C Thomas, 1933. Price, \$2.00.

PROMPTED by the desire to learn and describe "Something of the contributions of American physicians to obstetrics," the author has gathered together interesting material on the colonial midwifery system and on Shippen, James Lloyd, Bard, John Stearns, Dewees, Oliver Wendell Holmes, M. B. Wright and Walter Channing. The first obstetrical teaching, the first American textbook, "pulvis parturiens," difficult parturition, the contagiousness of puerperal fever, cephalic version, etherization in childbirth and the anemia of pregnancy are topics which one naturally looks for and finds. The only criticisms that arise are about the relatively high price and regret that the text is not twice as long. E. K.

PAPERS RELATING TO THE PITUITARY BODY, HYPOTHALAMUS AND PARASYMPATHETIC NERVOUS SYSTEM. By HARVEY CUSHING, Professor of Surgery (Emeritus), Harvard University; recently Surgeon-in-Chief, Peter Bent Brigham Hospital, Boston. Pp. 234; 99 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, \$5.00.

OUR knowledge of the pituitary, the most inaccessible and perhaps the most complicated of the endocrine glands, has been changing and expanding rapidly in recent years, due in no small measure to the author's own contributions. This expansion of 4 lectures delivered in 1930-1932 is an accurate, thoughtful and suggestive statement of these advances, though, as the author is the first to recognize, "it is quite probable that many of the interpretations are based on false premises and that even those which appear to be more securely grounded will not stand the test of time." In fact, some might well have already been modified: The Camus-Roussy and Bailey-Bremer doctrine of polyuria production by tuber cinereum lesions, for instance, without regard to the intrinsic defects in their evidence seems sufficiently negated by the line of thought here presented to have been given its historical value only. Although the mode of presentation adopted necessarily produces overlaps and occasional demoted statements, the latter at least have been well taken care of by textual or footnote insertions between square brackets. Most interesting in the book, as always, is the author's unique style, with its skillful use of the historical approach, its clarity of picturesque diction and pleasant inter-

ruptions with appropriate generalizations. Even his *confessio* of frank belief in teleology in nature is done with minimal irritation. Most important in the subject matter is the bulk of the first lecture, deriving from the tangle of contradictory evidence about the three pituitary lobes and their diencephalic connections a logical and convincing statement (summarized on page 57) about the functions involved. The lecture on the basophilic adenomas (lesions first described by Erdheim in 1903) puts this latest pituitary syndrome squarely on the map. As a clinicopathologic description, it leaves little to be desired. The physiologist, neurosurgeon, endocrinologist and intern can no better afford to be without this book's help than the surgeon can do without his textbook of anatomy.

E. K.

A CRITIQUE OF SUBLIMATION IN MALES: A STUDY OF 40 SUPERIOR SINGLE MEN. By W. S. TAYLOR, Professor of Psychology, Smith College. Pp. 115. Worcester, Mass.: Clark University Press, Genetic Psychology Monographs, 1933. Price, \$2.00.

THE author's effort has been to test the validity of the psychoanalytic theory of "sublimation," which, as he understands it, is the turning of "sex energy" from its natural outlet into intellectual, artistic and other "higher channels." This, it is alleged, has been done by some artists, philosophers and saints.

Accepting the theory in its entirety, only physically able, socially normal and mentally superior men were selected for questioning. The answers submitted by each individual showed an unsublimated quantum of sex expression in one or more forms, termed "adjustment." The several "adjustments" were: nocturnal emissions, erotic fondlings ("spooning," "necking" and "petting"), masturbation and resort to prostitutes and other women. The sex expression in order of frequency was as follows: masturbation, nocturnal emissions, erotic fondlings, prostitutes and women other than prostitutes. It is admitted that this analysis has not yielded finality.

Support is lent to the old faith in early marriages. In college, young married couples appear to be more contented and more successful. Economically, "if it is not true that two can live as cheaply as one, it is nevertheless true that two can live as cheaply as two."

N. Y.

CLINICAL PHYSIOLOGY OF THE EYE. By FRANCIS HEED ADLER, M.A., M.D., F.A.C.S., Instructor in Physiology and Ophthalmology, Medical School, University of Pennsylvania; Assistant Surgeon, Wills Hospital. Pp. 406; 92 illustrations. New York: The Macmillan Company, 1933. Price, \$5.00.

THIS book fulfills a need: before its appearance there was not available a text in the English language on the physiology of the eye sufficiently extensive to be of use to both the physiologist and the practising ophthalmologist. The author, who has happily combined the clinical aspects of ophthalmology with the experimental side of the physiology of the eye, is peculiarly qualified to write such a book. As he states in the introduction he has endeavored to write "a small textbook, giving in as simple terms as possible the fundamental facts and generally accepted theories of how the eye functions." The Reviewer believes that the author has fully accomplished his purpose.

The table of contents, better than further general discussion, may best convey the scope of the book. There are chapters on the protective

mechanism of the eye, the iris and pupil, accommodation, the lens and vitreous, visual acuity, visual pathways and visual fields, the objective changes in the retina due to light, the subjective characteristics of vision, binocular vision, entoptic and allied phenomena, the optic nerve, external ocular muscles, aqueous humor and the intraocular pressure. At the end of each chapter there is a very useful list of references to guide the reader who would pursue the subject further. The illustrations, many of them simple diagrams, are a valuable addition to the text. The style is clear and readable. This book will be welcomed by all who in practice or research are interested in the function of the eye under normal and pathologic conditions.

B. L.

CRIMES AND CRIMINALS. By WILLIAM A. WHITE, A.M., M.D., Sc.D.
Pp. 276. New York: Farrar & Rinehart, 1933. Price, \$2.50.

AFTER 40 years' practice in psychiatry with intimate contact with the criminal insane, the writer complains of the inadequacy of the law to meet the requirements of criminology and, among other reforms, recommends abolition of capital punishment. Clarence Darrow goes farther and asks that all prisons be done away with. In the past, Russia, Austro-Hungary and a part of Italy abandoned capital punishment but all returned to it later. In this country the maximum punishment is exacted with less and less frequency and our criminal population is constantly growing. The author was more familiar with criminals who were insane than with those who were not; he should observe the convicts during a prison riot.

In wars millions of good men are obliged to march to one another's destruction, and if it is right—or under the circumstances necessary—to kill so many good men, it cannot be entirely wrong to kill a few bad ones. The eminently sound and kindly William Howard Taft was right when he said: "We are pampering our criminals." An intellectual criminal once remarked to the Reviewer: "That there is honor among thieves is the one good joke accredited to the underworld."

N. Y.

THE GOLD-HEADED CANE. By WILLIAM MACMICHAEL, M.D. Edited with Explanatory and Illustrative Notes and an Essay on William MacMichael, M.D., His Life, His Work and His Editors by HERBERT SPENCER ROBINSON. Pp. 223; illustrated. New York: Froben Press, Inc., 1932. Price, \$5.50.

THIS is the 6th and latest edition of that celebrated account of the passage of the cane through the hands of five of England's most famous physicians. A portrait, biography and bibliography of the author together with specimens of his handwriting add considerably to the interest of this edition.

E. K.

THE TIDES OF LIFE: THE ENDOCRINE GLANDS IN BODILY ADJUSTMENT. By R. G. HOSKINS, Ph.D., M.D., Director of Research, Memorial Foundation for Neuroendocrine Research; Research Associate in Physiology, Harvard Medical School. Pp. 352; illustrated. New York: W. W. Norton & Co., Inc., 1933. Price, \$5.50.

For some years it has become increasingly apparent that the control of the body exerted by the endocrines in health and disease is of constant and utmost importance. The dramatic nature of endocrine disorders and of endocrine therapy and the complexity of their interrelationships, however, have led to so much romance in endocrin literature that skepticism

has encouraged and more than one conservative scientist repelled into other fields. A restrained statement such as the present one, accurately and ably compiled by a master student of endocrinology, is therefore to be welcomed as an especially important contribution. Its eliability can safely be guaranteed and on points where our knowledge is still hazy the author makes sure to point this out. Though written clearly and with excellent selectivity, the subject from its very nature will not furnish easy reading for the general reader. To those who are willing to bend their energies to its mastery, the reward will be considerable.

E. K.

HOEBER'S SURGICAL MONOGRAPHS. THE DUODENUM. ITS STRUCTURE AND FUNCTION, ITS DISEASES AND THEIR MEDICAL AND SURGICAL TREATMENT. By EDWARD L. KELLOGG, M.D., F.A.C.S., Professor of Surgery, and Formerly Professor of Gastro-enterology, New York Polyclinic Medical School, etc. With a Foreword by GEORGE DAVID STEWART, M.D., F.A.C.S., New York. Chapter on Duodenal Parasites by BAILEY, K. ASHFORD, M.D., Sc.D., Professor of Tropical Medicine and Mycology, University of Puerto Rico and Columbia University, New York, etc. Section on Roentgen Ray Diagnosis by A. JUDSON QUIMBY, M.D., Professor of Roentgenology, New York Polyclinic Medical School. Pp. 855; 287 illustrations, 3 in color. New York: Paul B. Hoeber, Inc., 1933. Price, \$10.00

THE delightful foreword to this monograph was written by George David Stewart, whose unfortunate death has just occurred. The author, who has for some years been making contributions to the subject of this book, has here for the first time in English dealt thoroughly with the anatomy, physiology, bacteriology and various diseases of the duodenum, as well as their treatment. There are 131 pages of references which is the most complete bibliography which the Reviewer has seen. The illustrations are numerous and excellent. Of the twenty-six chapters, the chapter on Physiology was written by Professor A. C. Ivy, while Dr. F. M. Jefferies prepared the text dealing with laboratory procedures.

While it may be considered by some that this is purely a monograph for surgeons, since it is one of a series of surgical monographs, it covers the medical diseases of the duodenum thoroughly. The author does, however, suggest rectal feeding in the treatment of duodenal ulcer, disregarding recently published data to the effect that this method is of little practical significance. He also omits the Andresen diet for bleeding duodenal ulcer. These are, however, small errors when one looks at the book as a whole.

The subject matter on duodenal ulcer is presented fairly and without bias, even though the author is a surgeon! I am sure that this monograph will be well received. It will remain for years to come as a classic on its subject. There will be few internists, specialists, or surgeons who will want to be without it.

I. R.

INTERNATIONAL CLINICS. VOL. I, FORTY-THIRD SERIES, MARCH, 1933. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, with the collaboration of twelve associates. Pp. 305; 16 illustrations, 1 colored plate. Philadelphia: J. B. Lippincott Company, 1933. Price, Cloth, \$3.00.

THIS volume is the first of a new series appearing after a complete reorganization with a new editor and a new list of collaborators, all prominent

medical names of this country, Canada and abroad. The object of International Clinics of bringing to the practitioner in the form of clinics, clinical lectures and reviews the latest information about current medical thought and practice, will be well attained if the standard of excellence of the present volume is maintained. The names of the new editor and his 12 collaborators should guarantee this maintenance, if their contact continues to be an active one. Although the title page continues to advertise "by leading members of the medical profession throughout the world," we note that only two of the collaborators are not of this continent and all of the 19 articles are by Americans. Though excellence is to be preferred, regardless of origin, we hope that the former international character of the journal will be retained.

E. K.

PROCEDURES IN TUBERCULOSIS CONTROL FOR THE DISPENSARY, HOME AND SANATORIUM. By BENJAMIN GOLDBERG, M.D., F.A.C.P., F.A.P.H.A., Associate Professor of Medicine, University of Illinois; Formerly Medical Director and Member and Secretary, Board of Directors, City of Chicago Municipal Tuberculosis Organization. With a Chapter on Sanatorium Planning by THOMAS KIDNER, New York City, and an Introduction by DAVID J. DAVIS, M.D., Ph.D., Dean of the College of Medicine, University of Illinois, Chicago. Pp. 373; 54 illustrations. Philadelphia: F. A. Davis Company, 1933. Price, \$4.00.

TUBERCULOSIS is here considered from the viewpoint of the public health official. Measures used to prevent the transmission of this disease, especially those adopted in Chicago, are described. In the first section there are chapters on special tuberculosis problems such as disease in the Negro and the Mexican; on tuberculosis legislation; and on establishment and operation of tuberculosis dispensaries, examination of contacts, epidemiological surveys, etc. The second section deals with the factors involved in the successful treatment of tuberculous patients in their homes. It is recognized that the sanatorium can accommodate only a small percentage of those who need treatment. In the third section there is a very complete discussion of the establishment and operation of tuberculosis sanatoria, sanatorium treatment and convalescent care.

This book is of little value to the student seeking to learn the symptoms, physical signs, differential diagnosis and treatment of pulmonary tuberculosis. But to social service and public health workers interested in the control of tuberculosis, it can be well recommended.

H. H.

CHRONIC ARTHRITIS AND FIBROSITIS. By BERNARD LANGDON WYATT, M.D., F.A.C.P., Director, The Wyatt Clinic, etc. Pp. 201; 17 illustrations. Baltimore: William Wood & Co., 1933. Price, \$3.50.

THIS little book is chiefly a collection of the studies and views of others. The text consists, in large part, of actual citations taken from original articles and various standard works. To the extent that the book reflects the increasing interest being shown in the field of arthritis it may serve a useful purpose. It further reflects, to some degree, the wider-angled outlook upon the subject now undeniably gaining ground.

Therefore to those unfamiliar with the rheumatoid syndrome, it may serve as an introduction. To the critical observer the book plainly reveals a purely clinical experience in this field and the author makes the mistake of introducing a classification of his own, rather than accepting the almost

universally adopted separation of chronic arthritis, based on morphologic data, into two groups, atrophic and hypertrophic. The type is good and the book is light in weight, a feature all too rare in American publications.
R. P.

DISEASES OF THE HEART. By SIR THOMAS LEWIS, C.B.E., F.R.S., M.D., D.Sc., LL.D., F.R.C.P., HON. D.Sc. (MICHIGAN), Physician in Charge of Department of Clinical Research, University College Hospital, London, etc. Pp. 297; 44 illustrations. New York: The Macmillan Company, 1933. Price, \$3.50.

THE success of the author's small books on Clinical Electrocardiography and Clinical Disorders of the Heart Beat clearly indicated that a similar book on general diseases of the heart would and should be forthcoming. In the present work common forms of heart disease and the information to be gained from physical signs have been stressed; a laudable purpose that has been aided by the rather novel arrangement, based more on disordered function than on structure. Thus after several chapters on the signs of cardiac failure, their cause, detection, significance and treatment, 2 short chapters follow on coronary thrombosis and angina pectoris. The disorders of mechanism are condensed into 34 pages and heart block combined with syncope. Rheumatic heart disease occupies 17 pages, compared to 6 of congenital malformations; while syphilis has 14, compared to 11 of pericarditis. Such condensations necessarily involve penalty; thus we find no mention whatever of tuberculous pericarditis; though a full page is given to Persistent Ductus Arteriosus, Fallot's Tetralogy and the useful grouping of congenital cases according to absent, tardy or constant cyanosis are conspicuous by their absence. While such omissions should not militate against a book which will undoubtedly be of great service and popularity, we cannot help but exclaim—a little more, and how much better! E. K.

FOOD IN HEALTH AND DISEASE. By KATHERINE MITCHELL THOMA, B.A., Director of Dietetics, Michael Reese Hospital, Chicago. Pp. 370. Philadelphia: F. A. Davis Company, 1933. Price, \$2.75.

THIS book is for student nurses and others interested in dietetics. Of its four parts, Part I is devoted to food and food requirements of normal individuals; Part II to diets in disease; Parts III and IV contain laboratory lessons for the study and preparation of various foodstuffs for the well and sick. The subject matter is well arranged and up to date and presented in a lucid, concise manner. This volume is recommended to those interested in this field.
L. J.

FORTY YEARS OF PSYCHIATRY. NERVOUS AND MENTAL DISEASE MONOGRAPH SERIES No. 57. By WILLIAM A. WHITE, A.M., M.D., Sc.D. Pp. 154. Washington, D. C.: Nervous and Mental Disease Publishing Company, 1933. Price, \$3.00.

REGARDING "insanity" as a purely social and legal term indicating a degree of maladjustment that requires special attention, the author undertakes to describe what has happened in its care during the forty years in which he has been actively concerned with it and to evaluate the gigantic progress that has been accomplished in this phase of man's understanding of man. Fortunately rich in autobiographical details—personalities furnishing to most of us more interesting reading than abstract ideas—the

book gives a wise mind's views on mental hygiene, psychoanalysis, medical psychology, mental hospitals administration, relations with the law and other problems that are now chiefly occupying this rejuvenated, active and most important of specialties. We heartily agree with his insufficiently appreciated view that "every physician ought to go into the community as well grounded in psychiatry as he is in the principles of obstetrics, pediatrics, surgery, and other medical specialties." E. K.

BINOCULAR VISION AND THE MODERN TREATMENT OF SQUINT. By MARGARET DOBSON, M.D. (LOND.), Ophthalmic Surgeon to the New Sussex Hospital for Women and Children, Brighton; Oculist in Charge of the Kilburn (L. C. C.) Eye Clinic. Pp. 107; 32 illustrations. New York: Oxford University Press, 1933. Price, \$2.75.

THIS small book aims to give the principles and practice of modern orthoptic training. The author considers that, as a result of exercise, the amblyopia of the squinting eye may be overcome, and in many cases by appropriate fusion training the squint may lessen or actually disappear.

The first three chapters deal largely with the author's ideas regarding the phorias and tropias. The last four are chiefly descriptions of instruments designed to carry out orthoptic training.

Many of the author's theories and practices will not be accepted by American ophthalmologists; but since there has been a constantly growing demand on the part of the public for information regarding "eye exercises," it may be well for physicians in this country to become acquainted with the methods used. It is unfortunate that treatments of this character lend themselves so readily to use by charlatans and honest but misguided doctors; there is, however, no doubt that some of the forms of exercises described are helpful adjuncts to our present methods of treatment. F. A.

BOOKS RECEIVED.

NEW BOOKS.

The Operative Story of Cleft Palate. By GEORGE MORRIS DORRANCE, M.D., F.A.C.S., Professor of Maxillo-facial Surgery, The Thomas W. Evans Museum and Dental Institute, School of Dentistry, University of Pennsylvania; Surgeon to St. Agnes' Hospital, and to the American Oncologic Hospital, Philadelphia. Assisted by ENAYAT SHIRAZY, D.D.S. Pp. 564; 534 illustrations. Philadelphia: W. B. Saunders Company, 1933. Price, \$6.50.

Nosokomeion. Quarterly Hospital Review No. 2, April, 1933, Containing the Proceedings of the Third Hospital Congress. Pp. 441. Stuttgart: W. Kohlhammer, 1933.

Nutrition. Vol. X of *Clio Medica*. By GRAHAM LUSK, Sc.D., M.D., LL.D., Late Professor of Physiology, Cornell University Medical College, New York; Former Member, Royal Society; Corresponding Member, Preussische Akademie der Wissenschaften. Pp. 142; 13 illustrations. New York: Paul B. Hoeber, Inc., 1933. Price, \$1.50.

The Medical Clinics of North America. Vol. 17, No. 1 (New York Number—July, 1933). Pp. 324; 64 illustrations. Philadelphia: W. B. Saunders Company, 1933. Price: Paper, \$12; Cloth, \$16.

- The Surgical Clinics of North America.* Vol. 13, No. 3 (*Lahey Clinic Number—June, 1933*). Pp. 275; 98 illustrations: Philadelphia: W. B. Saunders Company, 1933.
- The Nature of Disease Journal, Vol. II.* By J. E. R. McDONAGH, F.R.C.S. Pp. 197. London: William Heinemann, Ltd., 1933. Price, 7s 6d, net.
- History and Source Book of Orthopaedic Surgery.* By EDGAR M. BICK, M.A., M.D., Adjunct Orthopaedic Surgeon, Hospital for Joint Diseases, New York City; Adjunct Orthopaedic Surgeon, Montefiore Hospital, etc. Pp. 254; illustrated. New York: The Hospital for Joint Diseases, 1933. Price, \$1.50.
- Histopathology of the Peripheral and Central Nervous Systems.* By GEORGE B. HASSIN, M.D., Professor of Neurology, University of Illinois, College of Medicine; Attending Neurologist, Cook County Hospital, Chicago. Pp. 491; 229 illustrations. Baltimore: William Wood & Co., 1933. Price, \$6.00.
- The Therapeutic Agents of the Quinoline Group.* By W. F. VON OETTINGEN, M.D., PH.D., Assistant Professor of Pharmacology, School of Medicine, Western Reserve University, Cleveland. Pp. 301. New York: The Chemical Catalog Co. Inc., 1933. Price, \$6.00.
- The Doctrine of the Healing Power of Nature Throughout the Course of Time.* By MAX NEUBURGER, M.D., PH.D., Vienna. Translated by LINN J. BOYD, M.D., F.A.C.P., New York. Pp. 184. n.p., n.d. (New York, 1933).
- Frontiers of Medicine.* (A Century of Progress Series.) By MORRIS FISHBEIN, M.D., Editor, Journal of American Medical Association, and Hygeia, the Health Magazine. Pp. 207. Baltimore: The Williams & Wilkins Company, 1933. Price, \$1.00.
- Sane Sex Life and Sane Sex Living.* By H. W. LONG, M.D. With a Special Introduction by W. F. ROBBE, M.D. Pp. 151. New York: Eugenics Publishing Company, Inc., 1922. Price, \$2.00.
- On Phasic Introductory and Release Effects of the Cocaine Group on Vessel Preparations and an Attempt at a General Appraisal of Phase Effects.* By EDUARD RENTZ, Riga. Translated and Abstracted by LINN J. BOYD, New York: n.p., n.d. (New York, 1933).
- Health and Environment.* (Recent Social Trends Monograph.) By EDGAR SYDENSTRICKER. Pp. 217; 50 illustrations. New York: McGraw-Hill Book Company, 1933. Price, \$2.50.

NEW EDITIONS.

- Manual of Veterinary Bacteriology.* By RAYMOND A. KELSER, D.V.M., A.M., PH.D., Major, Veterinary Corps, United States Army; Officer in Charge, Veterinary Laboratory Division, Army Medical School, etc. Pp. 552; 93 illustrations and 11 tables. Second Edition. Baltimore: The Williams & Wilkins Company, 1933. Price, \$5.50.

In the vast domain of veterinary bacteriology, so largely unexplored, a comprehensive treatise is still a practical impossibility. The present work, however, not only helps to fill a wide gap—there being only one other recent work on the subject in English—but presents in compact space a wealth of material that has been assiduously prepared and kept up to date. It should be indispensable to those engaged in most kinds of veterinary and public health work.

- The Biology of the Protozoa.* By GARY N. CALKINS, PH.D., Sc.D., Professor of Protozoology, Columbia University. Pp. 607; 223 illustrations, and 2 colored plates. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1933. Price, \$7.50.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Idiopathic Hypochromic Anemia.—WINTROBE and BEEBE (*Medicine*, 1933, 12, 187) thoroughly discuss this so-called new type of anemia which has aroused considerable interest among hematologists the past 3 years. The report is based upon those cases which have appeared in the literature, together with a study of their own 25 cases. Ninety-six per cent of the patients have been women and 82 per cent were between the ages of 20 and 50 years, very few having had their menopause. The type is asthenic and a familial incidence is not unusual. In certain instances inadequate convalescence from pregnancy might be an initiating factor. The disease is always insidious in onset and may be expressed by a variety of subjective symptoms, none of which differs much from those which occur in any type of anemia. The physical examination is, however, quite characteristic. The waxy, bloodless appearance of the tired, apathetic woman, poorly constructed constitutionally, with papillary atrophy of the tongue and a certain number of instances with koilonychia, presents a rather typical picture. An almost constant observation is an absence of free hydrochloric acid and a low total acid with a marked deficiency of the hemoglobin, together with an invariable reduction in the size of the red cells. As a consequence the volume of packed red cells, the mean corpuscular volume and the mean corpuscular hemoglobin are all greatly reduced. There is no evidence of increased blood destruction. A striking feature is the magnificent response to iron therapy and the utter valuelessness of liver extract and desiccated hog stomach. The iron must be continued over a long period of time and in large doses. Bloomfield has doubted the authenticity of this syndrome and a number of writers have suggested that chlorosis and idiopathic hypochromic anemia are one and the same. The authors' answer to Bloomfield's objection is not entirely convincing, nor are they impressive in their dismissal of chlorosis as being a possible factor in the genesis of the condition. They suggest that the lack of free hydrochloric acid and low total acid may alone be the fundamental disorder in this type of anemia. Probably the best hypothesis, they indicate, to explain the pathogenesis of idiopathic hypochromic anemia is one of defective gastric secretion in an individual who loses blood, repeatedly at the menses or during pregnancy, who is unable properly to synthesize hemoglobin from the diet.

SURGERY

UNDER THE CHARGE OF

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The Symptoms Resulting From the Bite of *Latrodectus Mactans*.—
(See also article by J. WALSH and W. G. MORGAN on "Arachnidism; Report of a Series of 29 Cases of Poisoning from the Bite of the *Latrodectus Mactans*," in this issue.) A correct diagnosis in patients with acute abdominal symptoms is often difficult due to variations from the classical clinical picture of the various disease entities encountered. While exact diagnoses in this region are important, the most urgent decision which has to be made is whether or not the condition requires an immediate laparotomy. For this reason the symptom complexes of acute non-surgical abdominal conditions are of primary interest to the surgeon. A condition of this type results from the bite of the black spider, *Latrodectus mactans*. While the occurrence of arachnidism is undoubtedly rare in urban practice, the fact that within a period of a little over 1 year 6 such cases were treated in the University of Virginia, and 29 collected in the Walsh and Morgan series, indicates that in less thickly populated areas it is not a rare condition. Commenting on the 6 cases MORTON (*Arch. Surg.*, 1933, 26, 64) points out that even without a history of the bite of a spider the diagnosis is not difficult if one keeps the possibility of the condition in mind, but that one may just as easily make the mistake of regarding the condition as a surgical one if not familiar with the signs and symptoms of the condition.

The patient may or may not be aware that he has been bitten and it may be difficult to find the wound, even by thorough inspection. All the patients reported by Morton had severe cramping pains and rigidity throughout the abdomen. Tenderness was not commensurate with the degree of rigidity, and in addition there was pain or aching in the muscles of the back and thigh. The pain usually starts in a few minutes to an hour. The temperature rises to about 99° and 100° F. The leukocytosis may reach 20,000, and the pulse rate and blood pressure elevated. Morphine may relieve the pain but not the rigidity. Nausea and vomiting are usually present.

The chief points of differentiation between arachnidism and an acute surgical abdominal lesion are the history of the spider bite, the generalization of the rigidity and pain, the difference between the degree of the tenderness and the rigidity, and the occurrence of pain in the back and sometimes in the legs.

The "black widow" or *Latrodectus mactans* is widely distributed throughout the United States but is more abundant in warmer sections of the country. Other cases reported within the last 2 years, in addition to Morton's, were described by CORNWELL (*Southern Med. and Surg.*, 1931, 93, 885) and TOLLESON (*J. Med. Assn., Georgia*, 1933, 22, 30).

These cases occurred in the South and were quite similar to those reported by Morton. BOGEN (*Arch. Int. Med.*, 1926, 38, 623) reported 15 cases of arachnidism occurring in Los Angeles.

The reader is referred to the article by Walsh and Morgan in the present issue of this Journal for further details.

THERAPEUTICS

UNDER THE CHARGE OF

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The Serum Treatment of Scarlet Fever and Erysipelas.—BAXTER (*Glasgow Med. J.*, 1932, 118, 361) presents the results of 2 extensive clinical studies on the efficacy of concentrated scarlet fever streptococcic antitoxins for that disease and of various serums and antitoxins in the treatment of erysipelas. To test the scarlet antitoxin he employed one of two standard commercial sera in a series of 120 cases selected because of their severity. The serum was injected intramuscularly, generally in a dose of 10 cc. Seventy per cent of the patients received serum before the fourth day of illness, and in this group 66 per cent made excellent recovery, while 34 per cent developed some complication. In the group receiving serum after the fourth day approximately one-half recovered without complications. While the group is too small to give satisfactory data on the influence of the antitoxin on mortality, the author feels that it is reasonable to believe that the deaths in this severe group would have been greater without the use of serum. No ill-effects were observed in any instance. In some of the graver cases a second dose of the serum was required. An initial rise of temperature following the injection of serum developed within 8 hours in approximately 90 per cent of the cases, following which the temperature dropped steadily for the next 24 to 36 hours. The fall of temperature was delayed in the most severe cases and in those in which treatment was not begun until after the fourth day of illness. In almost every patient there was a pronounced improvement in the circulation following the use of serum, but the most extraordinary change observed was the prompt and almost constant disappearance of the symptoms of toxemia. The rash disappeared within 12 hours in three-quarters of the patients and there was rapid subsidence of the throat manifestations. The incidence of complications seemed to be significantly reduced, and the required period of hospitalization was markedly shortened in 60 per cent of the cases, although these patients were not dismissed from the hospital before the usual period of time had elapsed. Only 14 per cent of the patients showed serum disease which was generally of mild nature and only 1 patient showed

a true relapse. For the treatment of erysipelas the following sera were tried: A polyvalent antistreptococcic serum, scarlet fever antitoxin of 2 different manufacturers, erysipelas antitoxin and diphtheria antitoxin. Satisfactory results were secured with only 1 of the 5 sera, namely, the scarlet fever antitoxin of Burroughs and Wellcome, and the results from erysipelas antitoxin were notoriously unsatisfactory. Efforts to limit the spread of erysipelas by the intradermal injection of one or other of the sera around the lesion were unsatisfactory and the treatment proved too painful to justify its further trial. Intramuscular administration of the serum, in doses ranging from 10 to 30 cc. of the B. and W. scarlet fever antitoxin alone, were followed in the majority of cases by a critical fall of fever with subsidence of toxemia, although the local skin lesion continued to spread with diminished intensity in 30 per cent of the cases after the injection of serum. The most satisfactory results were secured from the intravenous injection of from 20 to 30 cc. of the scarlet fever antitoxin which produced a critical fall of temperature and elimination of evidences of toxemia in the great majority of cases, however severely ill. In 60 per cent of the cases so treated the skin lesion began to subside within 24 hours after the critical fall of temperature. Desquamation began within 48 hours of the crisis. There were frequent immediate serum reactions in the form of rise of temperature, pulse and respiration rate following within 1 hour after the intravenous use of serum among the earlier cases, but this was largely avoided in the later ones by previous skin testing, warming the serum to blood temperature and its very slow administration. The incidence of complications was very greatly lessened in the treated group as compared to a control untreated group. Complication appeared in only 5 of 73 cases treated intravenously and in none of 41 treated intramuscularly. These complications included 1 case of tonsillitis, 1 of adenitis and 3 of abscess formation, while in the control group 2 per cent were complicated by nephritis, 2 per cent by endocarditis, 4 per cent by pneumonia and 30 per cent by abscesses. The average duration of hospitalization in control cases was 28 days as compared to an average of 15 days for patients treated with scarlet fever antitoxin.

Some Investigations on Irradiated Ergosterol.—In view of a number of conflicting opinions concerning the constitution, production, toxicity and therapeutic efficiency of crystalline vitamin D₂, WINDAUS and LÜTTRINGHAUS (*Deutsch. med. Wchnschr.*, 1932, 58, 1669) present a discussion of some of their own recent investigations as well as those of other workers. These show that the irradiation of ergosterol is capable of producing its conversion into a group of substances which are known as lumisterin, tachysterin, vitamin D₂, suprasterin I, suprasterin II, and an impure mother substance known as No. 248. The authors find that crystalline vitamin D₂ can be produced in proportions representing about 50 per cent of the original ergosterol and that the particular method and wave length of irradiation is of no importance save that it has a slight quantitative influence upon the production of vitamin D₂. They find that vitamin D₂ represents at least 90 per cent

and probably actually all of the antirachitic potency of irradiated ergosterol. They also find that it is easily produced in crystalline form, in which form it is quite stable. The question having been raised as to whether the toxicity of irradiated ergosterol was due wholly to the contained vitamin D, or was in part due to the other substances known to be present, is discussed by the authors who show, by their investigations, that the toxic action is chiefly inherent in vitamin D. They conclude, therefore, that there is no nontoxic antirachitic vitamin. However, quantitative studies on toxicity show that the crystalline vitamin D₂ is considerably less toxic in proportion to its antirachitic potency than is the impure irradiated ergosterol. The greater toxicity of the impure preparation is due chiefly to its content of tachysterin which is, while toxic, devoid of antirachitic activity. Finally, they point out that the ability to produce a pure crystalline vitamin D renders it no longer necessary to resort to biologic methods of standardization for the establishment of an antirachitic dose, since 1 mg. of this crystalline product represents 40,000 international antirachitic units. It would seem from these investigations that the crystalline product possesses the therapeutic advantage of a more favorable relationship between antirachitic potency and toxicity than exists in the cruder irradiated ergosterol.

Changes in the Blood Following General Quartz Lamp Irradiation.—

The results of investigations on the effect of quartz lamp irradiation may be summarized as follows: (1) In healthy animals and man it is ineffective. (2) In experimentally induced anemias it aids hemato-poiesis. (3) In human diseases the effect on red cell count and hemoglobin is conflicting. TEPLOFF and MESCHERITSKAJA (*Deutsch. Arch. f. klin. Med.*, 1932, 174, 399) studied this problem more thoroughly, on 2 young dogs, 2 healthy persons and 7 patients (5 diabetics, 1 with diabetes insipidus and 1 with polyneuritis). The measurements of the urobilin content of urine and feces, as well as the red cell count, hemoglobin content and number of reticulocytes in the blood were performed during a 6- to 7-day control period, during 3 to 4 weeks of irradiation and during a period of 6 to 7 days after the irradiation. Under such conditions both in animals and in man there developed, as judged from the increased urobilin content of the feces, an increased hemolysis. Simultaneously, as judged from the increased reticulocyte count, there occurs increased erythropoiesis. The hemoglobin content and red cell count remain essentially unaltered, but the formation and destruction of the blood take place more rapidly. Simultaneously with, or soon after, the cessation of the medication both the hemolysis and the erythropoiesis become normal or subnormal.

The Action of Metaphyllin (Euphyllin) on Cheyne-Stokes Breathing and Asthma of Cardiovascular Origin.—GUGGENHEIMER (*Ztschr. f. Kreislaufforsch.*, 1933, 25, 98) finds metaphyllin administered intravenously in doses of 0.48 gm. in 10 cc. of distilled water or of 20 per cent glucose solution to be a most effective remedy for the control of Cheyne-Stokes breathing and of cardiac asthma. In cases where the evidences of cardiac failure are pronounced it is advantageous to add

0.25 mg. of strophanthin to the dose to increase the efficiency of the heart. From his personal studies and an analysis of the literature on the pathologic physiology of these two conditions supplemented by a consideration of the pharmacologic actions of metaphyllin, the author concludes that the drug accomplishes its effects by a direct dilatation both of the coronary arteries and of the arteries supplying the respiratory center, thus improving by both mechanisms the blood supply to the center. He points out that there is also evidence to justify the belief that metaphyllin also diminishes the bronchospasm which may be present in cardiac asthma. Finally, it seems evident that the action of the drug is unrelated to its content of ethylene diamine and that it depends in part upon the theophyllin and in part upon the action of the compound as a whole.

PEDIATRICS

UNDER THE CHARGE OF
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Chronic Non-specific Nephritis.—ALDRICH and BOYLE (*J. Am. Med. Assn.*, 1933, 100, 1979) give a brief description of the clinical features exhibited by 40 children with chronic non-specific nephritis along with the results of treatment over 10 years with low-protein diets. After the institution of high-protein diets with high-vitamin content and with improved hygienic care, definite improvements were seen. After critical consideration of the clinical picture and pathologic anatomy of this disease the authors questioned some of the generally accepted theories as to its pathogenesis. It was noted that only an occasional patient with chronic non-specific nephritis gave a history of acute postinfectious nephritis at the onset and that even the patients most severely ill with postinfectious nephritis usually made complete and permanent recoveries. It seemed possible that a pathologic process of a more benign nature than the progressive sclerosis found in chronic non-specific nephritis. They began to think of chronic nephritis as a separate entity clinically and attempted to differentiate it even in its earlier stages before the chronicity alone established its nature. They attempted to find some other cause than microbial infection. In looking about it was noted that the cases were found in the dispensaries, and that it was very rare in the well-to-do. The patients were malnourished and surrounded by poor hygienic environment. As the patients were retrogressing a radical change was decided upon. All of the preconceived ideas of diet were discarded, and the children were treated as another group of undernourished children would be. They were given meat or eggs 3 times a day. Salt was allowed to all those who were not definitely edematous. All known vitamins were included in the diet. In addition every effort was made to improve the hygiene. The results following the change were very rapidly noticeable. In general neither the blood pressure nor the blood non-protein nitrogen values increased

with the change. While the albuminuria persisted in most cases, it tended to decrease in amount, and disappeared entirely in 3 cases. As a result of 2 years experience with this dietary and hygienic régime the majority of the patients have shown definite clinical improvement.

Systolic Murmurs in Children.—BASS, MOND, MESSELOFF and OPPENHEIMER (*J. Am. Med. Assn.*, 1933, 101, 17) studied 64 children with systolic murmurs, both organic and functional. The records of all the murmurs contained vibrations of high frequency. Of the functional cases 86 per cent showed high-pitched vibrations only, while organic cases had low- as well as high-pitched vibrations. This suggests an additional means of differentiating between the two types of murmurs. In seeking the cause of the admixture of low vibrations in the organic cases, several factors must be considered. In the valvular organic murmurs, the murmur originates at the site of the valvular apparatus. In mitral insufficiency the high ventricular pressure forces a stream of blood back into the auricle through a more or less narrow opening caused by a shortening of the valvular leaflets and their consequent inability to close completely. The intensity of the murmur will depend on the velocity, the pressure and the volume of the backflow, which plays on the free edge of the valve as a bow on the strings of a violin. From this point the vibrations are transmitted to the whole system of auricle and ventricle. Similar considerations are applicable to the case of aortic stenosis when a high pressure stream strikes against a narrowed aortic ring during ventricular systole. These organic murmurs are usually louder than the functional type, which often appear as soft blows. This in itself is undoubtedly a factor that accounts partly for the low pitched vibrations. The louder the murmur the wider will be the area indirectly set into vibration and the greater the mass of tissue affected. Living tissues are at best not ideal conductors, and the original murmur is distorted by an admixture of widely varying vibrations. Occasional components of low frequency are demonstrable in rather soft organic murmurs, and on the other hand may be lacking in the occasionally quite loud systolic murmurs at the pulmonary area, which are universally regarded as functional. Therefore, some additional factor besides the intensity of the murmur must be assumed to account for the presence of low-pitched vibrations in organic valvular cases. The authors set forth a theory that, in cases of valvular lesions, the volume of blood set in direct vibration together with surrounding portions of the wall of the heart is relatively large and therefore gives ample occasion for the production of vibrations of low frequency, some of which may lie even below the acoustic range. It also gives a hint as to the explanation why the non-organic or functional murmurs lack low-pitched vibrations. They believe that the latter murmurs may be caused by purely local disturbances which set up vibrations of only a limited area of heart muscle, in the immediate vicinity of the whorl.

Thrombosis of the Dural Venous Sinuses in Infancy and Childhood.—BYENS and HASS (*Am. J. Dis. Child.*, 1933, 45, 1161) present a series of 50 cases of sinus thrombosis, which they divide into two groups. A certain number of cases were attributed to infection. No etiology was assigned to the remainder. Those infants in whom thrombi of the

primary type developed had a number of characteristics in common. They were less than 30 months of age. They often suffered from acute nutritional disturbances. Dehydration consequent to vomiting and diarrhea was usually the only important physical finding. The thrombi, almost invariably during the first or second week of the disease, formed in the midportion of the superior longitudinal sinus and propagated so that stasis was produced and coagulation of the blood occurred in the tributary cerebral veins. The most important factors in determining the site of localization in the sinus were the anatomic features that favored slowing and eddying of the blood current and any disease that produced concentration of the blood and sluggish circulation. The clinical picture of primary thrombosis was very variable. The condition was rarely diagnosed. Symptoms referable to an intracranial lesion appeared only after the circulatory obstruction had produced pathologic changes in the meninges and cerebrum. Hemorrhages in the meninges and hemorrhagic necroses in the cerebral cortex did not always produce symptoms or suggestive physical findings. The development of convulsions during the course of an illness or even after recovery was of important diagnostic value. Symptoms of meningeal irritation or evidence of hemorrhage into the subarachnoid space were frequently overlooked. Several cases were diagnosed as encephalitis. Many patients with primary sinus thrombosis should survive, but certain sequelæ might be expected to follow. In some cases there would be no residual anatomic change. In others, there would follow organization, resorption and virtual disappearance of the thrombus with only a small amount of fibrous tissue to mark the site of the lesion. Hemosiderosis, cystic degeneration, gliosis, calcification and atrophy of portions of the brain might well be expected to occur in the weeks and months following the original disease. Canalized thrombi, fibrosis, hemosiderosis, partial obliteration of the subarachnoid space, subarachnoid cysts and groups of newly formed bloodvessels might eventually mark the sites of hemorrhages into the leptomeninges. Hydrocephalus might develop as the result of interference with the absorption of spinal fluid.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Subcutaneous Fat Necrosis of the Newborn.—In an attempt to clarify the various types of subcutaneous induration occurring in newborn or young children, Fox (*Arch. Derm. and Syph.*, 1933, 27, 237) divides the cases into four groups: (1) Adiponecrosis subcutanea neonatorum; (2) sclerema adiposum (sclerema neonatorum); (3)

sclerema edematosum (edema neonatorum), and (4) scleroderma. The first type of induration, subcutaneous fat necrosis of the newborn, is a self-limited, localized process affecting various-sized areas of the body, often in a fairly symmetrical manner. The lesions appear from 2 to 20 days after birth, appearing as deep-seated indurated areas varying in size from a split pea to lesions involving the greater part of the back and buttocks. The color at the outset is usually bluish-red, the skin returning to its normal color before the lesions have softened and disappeared. The most striking feature is the non-pitting induration of the subcutaneous tissue, which areas are fairly well defined and may or may not be movable on deeper parts. The lesions disappear completely in from 5 weeks to 5 months, only rarely leaving slight traces of atrophy in their wake. The general health of the infant remains undisturbed throughout the evolution of the process. Pathologically the process is essentially a necrosis of fat cells and an infiltration of epithelioid and giant cells. The most important etiologic cause is probably some form of trauma, as compression during birth and too vigorous methods of resuscitation. Sclerema adiposum (sclerema neonatorum) in contrast is seen chiefly in undernourished, debilitated and premature infants. It begins as an edematous swelling of the feet extending upward. Some cases are extensive while others involve only localized areas, all showing a characteristic pitting on pressure. The disease is usually fatal in from 4 to 5 days. Scleroderma of the newborn is an exceedingly rare disease and the diagnosis is only justified if the indurative process remains unchanged for a year or more. The author presents 5 case reports of subcutaneous fat necrosis with histologic study in 3.

Skin Changes in Chronic Encephalitis.—An attempt is made by HANTHAUSEN (*Acta Dermat.-Vener.*, 1932, 8, 408) to collect the various dermatologic accompaniments of chronic encephalitic states. The best known is a pronounced seborrhea, most conspicuous on the face, which looks as if it were smeared with grease. It is supposed that this is caused by a condition of irritation in the assumed vegetative centers of sebum secretion. Anomalies of pigmentation are also common, especially what has been termed "brown forehead ring." The author has also seen this lesion in other affections of the central nervous system. It resembles chloasma uterinum, but in its typical form is an arched band of hyperpigmentation 1 cm. broad situated on the forehead with the summit of the arch near the hair line and the ends fairly straight at the temples. Some cases show a more diffuse pigmentation over the face with free white islands of various sizes. Several unusual expressions of eczematoid dermatitis have been observed. The lesions are for the most part unilateral eczematoid patches with pseudosegmental distribution, fairly defined outlines often running in straight lines, all suggestive of a relationship to central vegetative centers. The author maintains that self-inflicted lesions of the skin (pathomimia of Rasch) are conspicuously common in chronic encephalitis, 5 cases being observed in a group of 50 such patients studied. It is probably another expression of changes of character seen among such patients. Several isolated examples of trophic lesions of the skin and a bizarre hypertrichosis of the crura were also observed.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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The Supports of the Uterus.—As a result of his studies of the gross and microscopic appearances of the paravaginal and parametrial tissues, KOSTER (*Am. J. Obst. and Gynec.*, 1933, 25, 67) concludes that there is no ligamentous tissue, which might by its presence be able to support the uterus, to be found in the base of the broad ligament. Such a structure is described in textbooks under the name of Mackenrodt's ligament, the cardinal ligament, the uteropelvic ligament or the infundibulopelvic ligament, and is supposed to be around or near the uterine vessels extending from the uterus out to the lateral pelvic wall. He states that the name ligament attached to any structure existing in the base of the broad ligament is a misnomer and is distinctly misleading. The uterus cannot depend for support on any structure to be found in the base of the broad ligament, running from the cervix out to the lateral pelvic wall, any more than it can on any of the tissues to which it is attached. From this statement it can be seen that the explanation of the development of prolapse and its cure, can no longer include a consideration of these so-called ligaments so that operations for the cure of prolapse of the uterus based upon shortening of such non-existing structures have no rational basis. No doubt those gynecologists who have been partial to such operations will be in violent opposition to the above statement, but it all boils down to what should be considered a ligament. No one questions the existence of areolar connective tissue in the parametrial tissues but the existence of true tough fibrous tissue such as is usually associated with the word ligament is indeed very doubtful.

Pelvic Sympathectomy.—Although the profession in this country has not shown much interest in pelvic sympathectomy it has frequently been performed in some European clinics. CORTE (*Zentralbl. f. Gynec.*, 1933, 57, 72, 77), of Lyon, has resected the presacral nerve in over 200 cases with results that appear to be very satisfactory. The operation is indicated for the relief of severe pelvic pain such as is experienced in the late stages of cancer of the cervix and also in the severe pain associated with functional dysmenorrhea which does not respond to the usual remedies. In this series the operation was performed for the relief of dysmenorrhea in 125 cases. The operation gave relief in severe cases of vaginismus and dyspareunia and seems to be of value in the treatment of various vasomotor diseases of the pelvic organs which are associated with leukorrhea and nervous hydrorrhea. He has never had any bad results which could be attributed to the operation such as bladder disturbances, menstrual difficulties, secondary trophic

changes in the vagina or vulva or atrophy of any of the genital organs. Since his first operation was performed more than 7 years ago, sufficient time has elapsed for any bad effects to appear. In 30 cases the patients have gone through pregnancy since operation without any complications and in no instance has an ectopic pregnancy occurred. To the gynecologist who intends performing this operation it is important to remember that the presacral nerve is not a single nerve but is in reality a sympathetic plexus, and in order to obtain the expected results all of the fibers of the plexus must be interrupted. This, however, is not difficult to accomplish if the technique described by the author is accurately followed.

OPHTHALMOLOGY

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Changes of the Optic Nerve Resulting From Pressure or Arteriosclerotic Internal Carotid Arteries.—SAPHIR (*Am. J. Ophthalm.*, 1933, 16, 110) reports the results of gross and microscopic studies of the optic nerves obtained at necropsy from 6 patients with marked sclerosis of the internal carotid arteries. In 4 an aneurysmal dilatation was present in 1 of the carotids. None of the patients had shown any clinical evidence of loss of vision. Grossly, the optic nerves showed in all cases distinct flattening, thinning and compression, especially in the portion between the carotids and the membranous optic canals. The aneurysms produced also actual medial displacement of the nerves. Hyperemia of the small veins in the superficial portions of the nerves was seen in some cases and also definite impressions from the aneurysms. Histologically, however, the changes in the nerves were relatively mild. The glial and connective tissue fibers were usually moderately increased. In some instances the central bundles of the nerve seemed to be compressed and smaller than normal. Any degeneration present was more pronounced in the central than in the peripheral bundles. A slight perivascular lymphocytic infiltration was found only occasionally. Reduction of the size of the nerve seemed to have occurred in the main without appreciable degeneration, but with occasional myelin sheath degeneration in the central bundles. The chiasmal and intraorbital portions of the nerves were found to be normal. The arterioles within the optic nerves were normal and the gross changes present seemed to be due entirely to the effects of direct compression and not to nutritional disturbances. What histologic changes were present would suggest the possibility of central rather than nasal hemianopic field disturbances. From his observations in these cases, the author doubts that visual disturbances in old persons should often be assumed to be due to pressure on the nerves by sclerosed internal carotid arteries.

The Results of Own Blood Injections Into the Anterior Chamber in Tuberculosis of the Anterior Segment of the Globe.—SCHIECK (*Klin. Monatsbl. f. Augenh.*, 1933, 90, 1) reports excellent results in the treatment of 14 cases of tuberculous iritis and iridocyclitis from the use of injections of the patients' own whole blood into the anterior chamber. The aqueous is withdrawn by means of a cannula and enough blood is injected to cover the surface of the iris and the pupil but not to fill the chamber completely. The patient is kept sitting up after the operation so that the blood settles into the lower part of the chamber and does not stay too long in contact with the lens capsule. So far, no untoward effect of the injections has been noted. Rise of tension has not occurred and no permanent clouding of the lens capsule has been noted. The effects have been uniformly good. The regression of the inflammation has been rapid, and so far there have been no recurrences in any of the patients treated by this method, an unusual course for tuberculous iridocyclitis in which recurrences are the rule. The patients all had positive tuberculin reactions and were treated with tuberculin also. The author thinks that the resistance of tuberculous iridocyclitis to ordinary methods of treatment is explained by the fact that none of the protective mechanisms of the blood are present in the aqueous. Patients with tuberculosis of the anterior segment of the eye are usually otherwise healthy and show no signs of tuberculosis elsewhere. Their blood must, therefore, contain adequate protective substances which are placed in contact with the diseased tissues when blood is substituted for aqueous in the anterior chamber. Injections of whole blood into the anterior chamber had no effect on a case of traumatic iridocyclitis, on a case of sympathetic ophthalmia, nor on 2 cases of tuberculous keratitis.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Dynamics of Nasal Respiration.—In seeking data concerning the physiology of nasal obstruction, KRIMSKY (*Arch. Otolaryngol.*, 1932, 16, 705) concluded that for its interpretation one is obliged to form one's own deductions about a condition that should convey a more definite picture than is offered at the present time; and that, consequently, the term "nasal obstruction," like "rheumatism," has become a frequent but loose expression to denote mild or severe degrees of nasal closure, and in a number of instances a mere subjective state not supported by clinical observation. The author believes, moreover, that "by creating an issue as to the importance of an intelligent approach to this important problem, much may be done to arrive at more definite indications for nasal surgical treatment for this condition, which in the present state of investigation cannot always stand the test of critical analysis. Two U gauges were required for the rhinometric tests—one containing water, for recording low pressures; the other containing mercury, for

forced pressure readings. Minutiae of technique and an outline of recording are presented. From the information obtained from observations made on 8 human subjects, such conclusions are reached as: (1) the dynamics of nasal function offers a vast field for clinico-physiologic research; (2) the rhinometric test is essentially differential; (3) a disturbance in the equilibrium of nasal pressures points to a mild or severe degree of nasal obstruction, depending on the extent of the changes in the natural and forced pressures, respectively; (4) a progressive nasal obstruction first affects the natural pressures, then the forced inspiratory pressures and, lastly, the forced expiratory pressure; (5) nasal obstruction, though not uncommon, is far less frequent than ordinarily suspected; (6) while a marked drop in the forced pressure points to nasal obstruction, one should bear in mind that asthenic states and pulmonary disease, such as emphysema, may render it impossible for the patient to generate a greater force; in these cases, too, the differential changes should guide one in determining the nasal condition; (7) oral records were not helpful in arriving at these conclusions and, finally, while pressure tests are too time-consuming to be advocated as a routine procedure, they have value under several circumstances, which the author tabulates.

RADIOLOGY

UNDER THE CHARGE OF

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Studies of the Effect of Irradiation on the Healing of Wounds.—POHLE and RITCHIE (*Radiology*, 1933, 20, 102) exposed 78 rats to Roentgen rays (100 KV, 2 mm. of Al) immediately, 24 hours and 48 hours following incisions in the skin of the back. Half of each wound was irradiated following the cutting and the other half was protected. Sections were made of specimens taken at daily intervals from 1 to 9 days after incision. Delay in healing was most constantly observed in wounds treated 24 hours after cutting. Histologically this became evident from 3 to 4 days after the cutting, but seemed most apparent after about 7 or 8 days. The irradiation seems to have less effect on the epithelium than on the underlying connective tissue.

Diagnosis of Uterine and Tubal Pathology Using Lipiodol.—HARRIS (*Radiology*, 1933, 20, 146), discussing the elementary features of utero-salpingography, regards it as an unrivalled means of establishing the diagnosis of uterine fibromyomas and pregnancy, and for determining the cause of sterility. When depicted by lipiodol the normal uterine shadow is triangular and the tubes appear as thin wavy lines extending to a widened ampulla. Occlusion of one or both tubes is often found

in cases of sterility. Intramural fibromas project into and deform the uterine shadow. Diagnosis of pregnancy, according to the author, can be made as early as 2 weeks after impregnation. The contour of the uterine triangle is deformed by the projection of the ovum, and both tubes are occluded. Although it is held that uterosalpingography is likely to cause abortion, the author feels that this will not often ensue if the introduction of the oil is stopped as soon as the patient complains of cramps.

The Roentgen Ray Evaluation of Breast Symptoms.—It is held by LOCKWOOD (*Am. J. Roent. and Rad. Ther.*, 1933, 29, 145) that the Roentgen examination of the breasts offers a high degree of accuracy in the diagnosis of cancer and other diseases. It is not offered as a substitute for other methods but as a valuable addition to them. In roentgenograms of chronic cystic mastitis the small cysts appear as clear areas 1 to 4 mm. in diameter; large cysts of the blue dome variety appear as large irregular clear spaces in the parenchyma. Cancer shows as a rather dense, irregular tumor often with a feathery periphery. The cancerous lymph node in the axilla is seen as a smooth, rather dense opaque area, whereas the inflammatory node is faint and irregular in outline.

NEUROLOGY AND PSYCHIATRY

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A General Symptom in Brain Tumor.—KLINKE (*München. med. Wchnschr.*, 1931, 77, 50) presents 4 cases of cerebral tumor in which Kehrer's two signs were demonstrable in unmistakable fashion. The first of these comprises the production of pain on deep pressure over the back of the neck, a little to one side of the mid-line, at the site of emergence of the great occipital nerve. Associated pain reactions consist in flushing of the face, and flexion of the head and neck backward and to the homolateral side. Kehrer's other sign consists of pain on deep pressure over the points of emergence of the three branches of the trigeminal nerve on the face. While this maneuver may cause pain on one side only, or perhaps merely in one or two of the branches in cases of tic douloureux and of migraine, in patients with cerebral tumor all six points are painful on pressure. The author believes that these are early and valuable signs of increased intracranial tension analogous to the demonstration of papilledema. He states that further research is required to determine which of the two signs can be elicited first and whether there is any correlation between priority of appearance and site of the neoplasm.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Cholesterin Content of Skin of Fetus and of Child in Relation to Solar Irradiation.—ROFFO (*J. de phys. et de path. gén.*, 1932, 30, 345) summarizes results of previous communications which indicate that cholesterin content of skin varies according to exposure to sunlight, regions freely exposed showing an increase, those kept in darkness a comparative diminution. The author now reports on determinations of cholesterin content of skin of fetus and young child. The cholesterin in skin of two regions—cheek and abdomen—was calculated. The average increase of cholesterin in skin of cheek of fetus compared with that of abdomen was 0.005 as compared with 0.07 in the infant of from 3 days to 3 years and 0.72 in the adult man. Moreover, skin of face of fetus and of child contains 1.24 times as much cholesterin as that of abdomen, that of adult man 3.53 times as much; or, if the increase be considered in percentage, the increase in the fetus is only 25 per cent and that of the child 39 per cent as compared with 253 per cent in the adult man. The slight difference of the proportions in the skin of the two regions in the fetus is attributed to the absence of solar irradiation during intrauterine life. The differences of cholesterin content of the skin in woman approach those of the child owing to protection given her skin. The cholesterin content of skin of forehead—a covered region of the face—is comparable to that of the abdomen. If the average of the figures for these two regions, especially in the skin of woman, is taken, the differential figures are slight, and close to those of the child and fetus. The author concludes that there is an increase of cholesterin in the skin of uncovered regions which is in proportion to age, and that this phenomenon is connected with the condensing action produced by the rays of the sun.

Human Experiments with *Brucella Abortus*.—In 1912 a review appeared in this Journal under the heading Infectious Abortion and its Relation to Man which suggested that the organism producing abortion in cattle might be capable of infecting man. Since then the human cases of infection with bacteria of this group have been frequently recognized, but whether the causative organism is the unchanged abortus bacillus discovered in 1897; a strain of *B. melitensis* (1889) of unusual distribution; or a race which passing through swine from cattle has adapted itself to the pig and incidentally has become more virulent for man as believed probable by THEOBALD SMITH (*J. Prev. Med.*, 1928, 2, 345) is still unsettled. Immunologic methods have indicated a close relationship for members of this group

but have not been helpful in discovering changes in virulence of these bacterial by passage through different hosts. *Brucella abortus* has been active in dairy herds since 1893, according to the evidence of Theobald Smith, but the reason for the increasing incidence of human infections is still puzzling. Human experiments on 40 volunteers were undertaken in Puerto Rico by MORALES-OTERO (*P. R. J. Pub. Health and Trop. Med.*, 1930, 6, 3) the various strains of the organs being given by mouth and through abraded and normal skin. Infections were established by both the mouth and the abraded skin. He was greatly impressed with the virulence of the porcine strains in man and with their ability to invade the gastro-intestinal canal in contrast to the inability of bovine strains to do so. In a later study (*J. Inf. Dis.*, 1933, 52, 54) he obtained further evidence that the strains of bovine origin are of low pathogenicity for man since 3 volunteers after ingesting infected milk for 6 weeks showed no symptoms nor other evidence of infection, nor in 2 other volunteers did the *Brucella abortus* cause an infection *via* the skin. This method of approach to a confused and intricate problem deserves attention despite the obvious difficulties involved in such studies.

Infection of Accessory Sinuses in Vitamin A Deficiency: The Rôle of Carotene in Infection of the Upper Respiratory Tract.—The important rôle of vitamin A in the prevention of infection, especially of the upper respiratory tract, upper digestive tract, nasal cavities and middle ear, is demonstrated by TURNER and LOEW (*J. Inf. Dis.*, 1933, 52, 102) Carotene is the plant source of vitamin A and is relatively unstable, being converted to achrocarotene with loss of color and potency. Using olive oil as a solvent promotes absorption from the intestine, and the addition of hydroquinone or quinhydrone stabilizes the solution for as long as 4 months. The effect of carotene on growth and general health is shown by an experiment on rats. One hundred albino rats were reduced to a xerophthalmic state by giving a vitamin-A-free diet and were divided into 4 groups for treatment. Group A, those receiving active carotene for the test period of 35 days, showed an average gain of 39 grams with cure of xerophthalmia. At autopsy the animals appeared healthy, showed few systemic conditions, and a small number of suppurative conditions of the nasal cavities and middle ear. Group B, those receiving weak or faded carotene, showed a loss of 69 grams in weight with only slight improvement in xerophthalmia. Autopsy revealed evidence of vitamin A deficiency and 100 per cent of positive cultures from the nasal apertures. Group C were negative controls, receiving only olive oil. These showed loss of weight and severe xerophthalmia. The animals were poorly nourished and showed 59 per cent systemic conditions. Group D were positive controls, receiving cod-liver oil, appearing healthy and with no signs of suppurative or systemic conditions at autopsy. The flora obtained from the nasal and aural conditions were staphylococci, colon bacilli, a Friedländer-like bacillus and *Micrococcus catarrhalis*. The carotene therapy reduces the number of spontaneous suppurative lesions of upper respiratory tract occurring in animals deprived of vitamin A. Xerophthalmia was cured in 100 per cent and normal health regained in 74 per cent.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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A Ten-year Study of Toxin-antitoxin Mixture and the Schick Test in the Control of Institutional Diphtheria.—YOUNG and CUMMINGS (*Am. J. Pub. Health*, 1932, 22, 1151) conclude from their studies that true or subclinical diphtheria may be a factor in maintaining a high degree of institutional immunity to the disease. The span of artificially produced immunity as measured by the Schick test approximates 7 years, immunized positives returning rapidly to the positive state in the following years. Natural or Schick negative reactors tend to return to the positive state with the elimination of the influence of true or subclinical diphtheria. Administration procedure should include Schick surveys on immunized groups coinciding with the decline in the general level of immunity. Schick surveys at intervals beyond the one over which the protection against diphtheria may be assumed should include original natural negative reactors as well as artificially immunized negative reactors.

The Infection of Cows With B. Abortus Variety of Brucella From a Public Health Standpoint.—WILCOX (*Am. J. Pub. Health*, 1932, 22, 1157) states that the milk of cows infected with the bovine variety of *B. abortus* is a potential source of infection for man. The danger of infection is relatively small when milk contaminated with the bovine variety is considerably diluted. *Brucella agglutinins* may be present in the blood of man due to the consumption of milk containing *B. abortus*. These antibodies may occur in the absence of clinical symptoms. Cows in whom abortions have occurred may develop immunity so that they calve normally and still continue to excrete *B. abortus* in their milk.

Diet, Nutrition and Infection.—HESS (*New England J. Med.*, 1932, 207, 637) states that the antirachitic factor, whether given as ultraviolet irradiation, as irradiated ergosterol or as cod-liver oil, does not increase the immunity of infants to respiratory infections. Respiratory infections are not due to a lack of vitamin A and generally cannot be lessened by giving a diet rich in this factor even when supplemented with cod-liver oil. The average infant seems to receive an adequate amount of vitamin A in its milk, judging by the fact that xerosis of the eyes is exceedingly rare, and that no gain in weight or increase in immunity is brought about by adding vitamin to the diet. The same

seems to hold true for older children and adults, in view of the infrequency of night blindness, the first sign of this deficiency. A lack of vitamin C may induce heightened susceptibility to infection of the respiratory tract. It may, however, induce merely local susceptibility without appreciable loss of systemic immunity. This peculiar phenomenon is manifested by the occurrence of typical nasal diphtheria, associated with virulent diphtheria bacilli, but a Schick reaction negative to highly potent solutions of toxin.

A Study of the Dissociation of the Rawlins Strain of *Bacterium Typhosum* With Special Reference to Its Use in the Production of Antityphoid Vaccine.—GRINNELL (*J. Exp. Med.*, 1932, 56, 907) studied subcultures of the Rawlins strain of *Bacterium typhosus* used by 12 different laboratories for vaccine production and found that they all differed from recently isolated smooth strains in cultural characteristics, virulence and protective efficiency. Eleven of these Rawlins cultures gave both the flagellar and the somatic type of agglutination in antismooth rabbit serum, and the 1 culture so tested produced both flagellar and somatic agglutinins when injected into rabbits and man. Agglutination of neither the flagellar nor the somatic type can, therefore, be used as a test of the smoothness of a culture or as an index of immunity. Since the Rawlins strain differs from the smooth phase of *Bacterium typhosus* in cultural characteristics and in virulence, and is much less efficient than smooth strains as a protective antigen; and since the selection and maintenance of smooth cultures suitable for vaccine production present no serious difficulty, it would seem but logical to substitute virulent, smooth cultures for the very old Rawlins strain, if we are to expect the maximum protection from antityphoid vaccination.

The Maternal Transmission of Vaccinial Immunity in Swine.—NELSON (*J. Exp. Med.*, 1932, 56, 835) found that the introduction of vaccinia virus into the skin of swine calls forth a typical vesicular reaction which may be followed by a solid immunity. This acquired state of resistance was utilized in determining the route of immunity transmission from sow to young. The suckling young of immune sows, vaccinated on the 7th day or earlier, showed no reaction to the virus. Their hand-fed litter mates, however, were susceptible and reacted with the formation of vesicles. These observations indicate that the porcine placenta is largely impermeable to protective substances and establish the fact that colostrum functions as the vehicle for their transmission as it does for antibodies.

The Rôle of Activated Milk in the Anti-rickets Campaign.—HESS (*Am. J. Pub. Health*, 1932, 22, 1215) states that activated milk, in the fluid or dry form, possesses the advantage not only of providing an automatic method of preventing rickets and of supplying this essential factor in a medium rich in phosphorus and calcium, but, as has been shown, it accomplishes this end by means of an exceptionally small amount of the antirachitic factor. In view of these important advantages the author recommends the general use of such milk for infants and children, especially in large communities. Whether adults, whose

bones are growing at a much slower rate, require a supplement of vitamin D to their dietary must be left undecided, to be answered according to the outcome of subsequent investigation. There can be little doubt, however, that the rapidly growing organism requires this factor and that, in the temperate zones, the infant and child do not receive the optimal amount from the radiations of the sun and from the meager supply in the food.

The Attenuation of Measles.—STEWART (*New England J. Med.*, 1932, 207, 780) believes that under conditions of private practice it is well worth while to protect the brothers and sisters of a child with measles by intramuscular injections of blood from some older member of the family who has had measles. This is especially true of the younger children. Unless a child is already seriously ill, it is wisest to attempt to produce an attenuated form of the disease, which presumably gives lasting immunity. Twenty cubic centimeters of whole blood can easily be injected without delay or complicated equipment. The history that a child has had measles should not be too thoroughly relied upon.

Pasteurization of Milk Artificially Infected With Two Strains of *Brucella Suis*.—PARK, *et al.* (*J. Bacteriol.*, 1932, 24, 461), found 2 strains of *Brucella suis*, in hermetically sealed glass tubes of whole milk (500,000,000 organisms per cc.), to be non-viable after 20 minutes at 140° F., after 15 minutes at 142° F., and after 7 minutes at 144° F. The same strains proved more resistant to heat in cotton-stoppered tubes of milk. *Brucella suis* survived for 30 minutes at 144° F. in milk containing 10,000,000 to 500,000,000 organisms per cc., but the same period of time at the same temperature destroyed *Brucella suis* in milk containing 5000 to 1,000,000 organisms per cc. Therefore, it appears that the thermal death time is influenced by the degree of contamination. The data suggest that efficient pasteurization will prevent milk-borne porcine brucellosis. However, final conclusions are withheld pending results of studies on commercial pasteurizers.

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ORIGINAL ARTICLES.

THE IMPORTANCE OF DEALING QUANTITATIVELY WITH
WATER IN THE STUDY OF DISEASE.*

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SEVERAL years ago while engaged in solving a clinical problem, we reached a stage at which no further progress could be made until we would be able to measure the exchange of water in 24 hourly periods for a number of days. It was already known that the organism not only takes in water as such from the outer world and as part of the food, but that water is also formed within the body by oxidation of hydrogen present in the metabolic mixture; further that if body tissue is being consumed, the water heretofore attached to it will be freed and added to the available supply. It was also a matter of common knowledge that water passed out of the organism as the chief constituent of the urine and stool. However, the magnitude of the loss of water by evaporation from the skin and lungs had received little consideration.

These various increments of water are given their proper places in Table 1.

* Presented to the Greater Boston Medical Society, March 7, 1933.

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TABLE 1.—INCREMENTS OF WATER EXCHANGE.

Available water.	Excreted water.
1. Exogenous	3. Urine
A. Diet	
B. Water as such	
2. Endogenous	4. Stool
A. Oxidation	
B. Preformed	5. Vapor

Standard laboratory methods permit the measurement of the exogenous supply of water. It is, however, only possible to determine how much is contributed by the two endogenous sources after it is known how many grams of protein, fat and carbohydrate were metabolized during the period. Similarly, on the outgoing side, no new methods were needed to deal with the water of the urine or stool. It was, however, necessary to develop a special technique in order to determine how much water had been vaporized from the skin and lungs.

Fortunately, Benedict¹ had just pointed out the quantitative relationship between the insensible loss of weight and basal metabolism. Further study on our part² showed that this phenomenon could be used as the key to the information needed in order to obtain a complete statement of the water exchange.

It is not our intention to enter into a discussion of the many and, at times, complicated physiologic principles that form the basis of the method employed to obtain the desired information about the various increments of water. Those who care actually to make the determinations will find a full description in our earlier papers. Our chief purpose is to show you how greatly one's understanding of disease is increased by a knowledge of the metabolism of water. We shall therefore present only the briefest outline of the technique by means of which the facts are obtained, and then devote the remainder of our remarks to an interpretation of such data.

Table 2 sets forth the steps that must be followed to obtain the weight of the water vapor and the composition of the metabolic mixture. By means of the initial and final body weights and the weights of the ingesta and excreta, the insensible loss of weight is calculated. This latter is the sum of the water vapor plus the difference between the weights of the carbon dioxide given off and the oxygen absorbed. This difference is mainly due to the metabolism of carbohydrate and amounts to 41 gm. for every 100 gm. of carbohydrate metabolized.* The subject (who has been on a fixed diet

* The respiratory exchange of protein is such that the metabolism of 100 gm. of it causes a difference of only 8 gm. between the weights of the carbon dioxide and the oxygen. The metabolism of fat, on the other hand, requires so much oxygen that it weighs 8 gm. more than the carbon dioxide for every 100 gm. of fat. The loss due to the former is opposed to the gain caused by the latter. Corrections for the small difference that may still exist, can be made, but are omitted here to avoid confusion.

for 3 preliminary days and continues to receive this diet) metabolizes as much carbohydrate as the diet contains. Hence, the weight of the water vaporized may be calculated as indicated by "C" in the table. This vapor carries away 0.58 calory per gram; and the heat thus removed is 24 per cent* of the total heat. Accordingly, the heat production for the period is obtained by the equation labelled "D." The composition of the metabolic mixture is now easily obtained. Its content of carbohydrate is already known. The amount of protein metabolized is calculated according to standard practice. The heat liberated by these two substances is subtracted from the total heat to secure that produced by the fat.

TABLE 2.—DETERMINATION OF METABOLIC MIXTURE.

A. Weights needed:			
1. Initial	2. Food plus	3. Urine plus	4. Final
Body weight	Water	Stool	Body weight
B. Insensible loss of weight:			
(1 + 2) - (3 + 4)			
C. Water vaporized:			
$B - (\text{Dietary carbohydrate} \times 0.41)$			
D. Heat production:			
$C \times 0.58 \times \frac{100}{24} = \text{Calories}$			
E. Metabolic mixture:			
Protein = Excreted nitrogen $\times 6.25$			
Carbohydrate = Same as diet			
Fat = $\frac{D - (\text{calories from protein} + \text{carbohydrate})}{9.5}$			

The water furnished by the oxidation of these substances is obtained by means of well established constants, as set forth in Table 3. Next it is necessary to compare the diet with the metabolic mixture to see whether body tissue has been destroyed or whether new tissue has been acquired. The amounts of water involved are then calculated by means of the constants found in the lower part of Table 3.

TABLE 3.—DETERMINATION OF ENDOGENOUS WATER.

A. Oxidation water:	
Protein	$\times 0.40$
Fat	$\times 1.07$
Carbohydrate	$\times 0.60$
Total	
B. Preformed water:	
Compare diet with metabolic mixture	
Protein	$\times 3.0$
Fat	$\times 0.1$

So much for the technique. Let us now examine the exchange of water in the case of normal persons whose activity is sufficiently

* The evidence upon which this statement is based is contained in our publication.

limited to make them comparable with patients. The relative weights of the various increments of water under such circumstances are indicated in Table 4. It should, however, be realized that the perfect balance achieved there is in fact uncommon. Normal persons as a rule either retain or lose a little water from day to day. They do, however, tend to strike a balance when the periods are lengthened to a week. Furthermore, the exogenous water varies considerably from day to day and the volume of urine rises and falls with it. Above all, the table makes it clear that both the water of oxidation and water vapor play a sufficiently important rôle in the exchange to justify the effort entailed in obtaining their actual weights. This is especially true for the water vapor.

TABLE 4.—WATER EXCHANGE—BALANCE.

Available water.		Excreted water.	
	Grams.		Grams.
1. Exogenous		3. Urine	1000
A. Diet	900		
B. Water as such	1100	4. Stool	200
2. Endogenous			
A. Oxidation	200	5. Vapor	1000
B. Preformed	0		
	<hr/>		<hr/>
Total	2200	Total	2200

The situation may be very different in disease. As is apparent from Table 5, the organism may lose a large amount of body water, even though much more water is available than in health. Or water may be added to the body, even though the available water is not large. Table 6 is an example of this phenomenon. Manifestly it would be quite impossible to detect these shifts in water balance by merely comparing the amount of fluid ingested or injected with the volume of urine. Thus in the first instance, an infusion of 3000 cc. of water was accompanied by a small amount of urine—700 cc. Nevertheless, the body water was diminished by more than 1 liter in 24 hours. On the other hand, an intake of only 1200 cc. of water and the output of 800 cc. of urine did not prevent the retention of more than 500 cc. of extra water in 24 hours.

TABLE 5.—WATER EXCHANGE—DEHYDRATION.

Available water.		Excreted water.	
	Grams.		Grams.
1. Exogenous		3. Urine	700
A. Diet	0		
B. Water as such	3000	4. Stool	750
		5. Vapor	1000
2. Endogenous		6. Emesis	1500
A. Oxidation	225		
B. Preformed	200	7. Drainage	750
	<hr/>		<hr/>
Total	3425	Total	4600

Daily dehydration, 1175.

TABLE 6.—WATER EXCHANGE—HYDRATION.

Available water.		Excreted water.	
	Grams.		Grams.
1. Exogenous		3. Urine	800
A. Diet	900		
B. Water as such	1200	4. Stool	150
2. Endogenous		5. Vapor	850
A. Oxidation	250		
B. Preformed	0		
		Total	1800
Total	2350		
Daily hydration, 550			

We turn now to another condition in which the study of water exchange has been very informative. You are familiar with the widespread belief that there are two kinds of adiposity, namely, "simple," which is nothing more than the expected result of over-eating; and "constitutional," which is attributed to some metabolic fault and is said to be little or not at all influenced by the calories of the food. A typical example of the experience upon which this belief rests is displayed in Fig. 1. An individual who requires 2300 calories to maintain weight is abruptly restricted to 1500 calories. She loses weight for the first 2 days but thereafter she continues

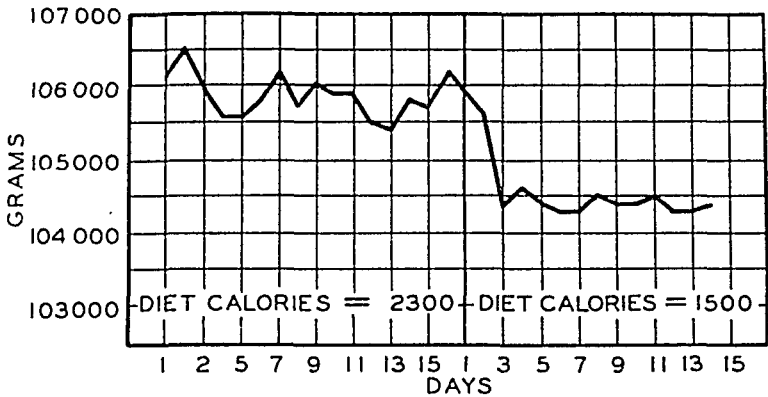


FIG. 1.—A subject who requires 2300 calories may not lose weight on 1500 calories.

to weigh the same, even though she is being underfed. There is, however, nothing specific about this phenomenon since one may obtain the same type of response from normal individuals, as is evident from Fig. 2. This normal man actually gained weight even though he was being underfed to the extent of 610 calories a day. Our studies showed that he was consuming 6 gm. of his body protein and 60 gm. of his body fat every day. The water hitherto attached to these substances would now be released. The sum of the two solids and the tissue water amounts to 90 gm. The loss of weight caused by the excretion of this material is indicated by the broken

line in Fig. 2; and this is to be compared with the actual course of his weight represented by the solid line.

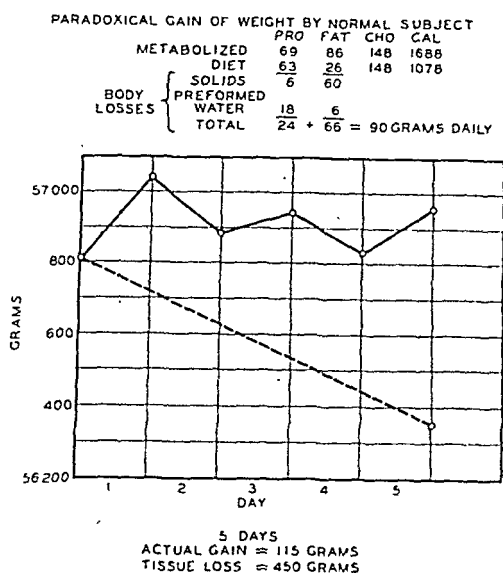


FIG. 2.—A normal man may gain weight while being underfed.

Table 7 makes it clear why this normal subject gained weight even though he was underfed. The destruction of 450 gm. of body tissue was accompanied by an addition of 115 gm. to his actual weight. It is accordingly necessary to account for the sum of these two, that is, 565 gm., in order to explain the paradox. Examination of the water balance shows that in fact he added 570 gm. of water to his body during this period. This retention of water accounts completely for the gain in weight under the circumstances. Since this phenomenon may be regularly produced in the normal subject, attempts to attribute it to inherent abnormalities of metabolism in the case of the obese, are wholly unnecessary.

TABLE 7.—RETENTION OF WATER CONCEALS DESTRUCTION OF TISSUE.

Date, 1929.	Change in weight of subject, grams.	Weight of body tissue destroyed, grams.	Water balance.
February 3	+ 285	90	+ 369
February 4	- 225	90	- 105
February 5	+ 65	90	+ 149
February 6	- 125	90	- 41
February 7	+ 115	90	+ 198
Totals	+ 115	450	+ 570

When the same type of study is applied to subjects who appear to be suffering from constitutional obesity, it is found that their

failure to lose weight is also entirely attributable to retention of water. Fig. 3 shows that such a person lost no weight for 16 consecutive days in spite of drastic underfeeding. It was, nevertheless, evident why this took place after a study of the water exchange demonstrated that she had retained nearly 3 liters of water during these 16 days. Similar studies led us to conclude that all obesity is simple obesity.

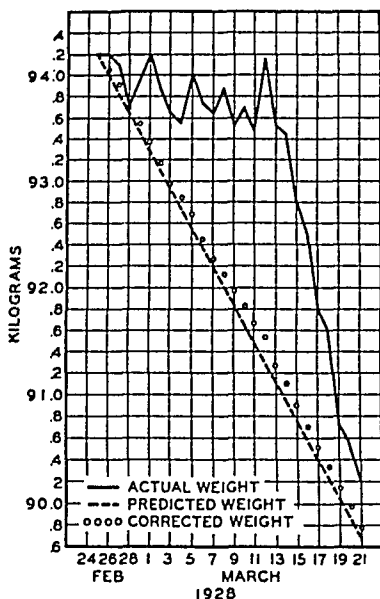


FIG. 3.—Failure to lose weight for 16 days by an underfed, obese subject is entirely explained by retention of water.

We are learning a great deal about disease of the kidneys by studying the water exchange. We will in the first place show you the response to restriction of water—Table 8. All the subjects received food selected for its dryness without any additional water. By this means the available water was reduced to about 700 cc. for each 24 hours. Under these conditions normal kidneys remove the 32 or 33 gm. of solid wastes contained in the diet in a relatively small amount of water because their kidneys can form highly concentrated urine. Nevertheless, they must dehydrate themselves to do so, for they continue to lose about a liter of water vapor daily, even though they drink no water. When next chronic nephritics who have no edema, are examined, it is found that they also rid their bodies of all the solid wastes. This is especially interesting since the more severe ones can no longer secrete a concentrated urine. They accordingly require more and more water to accomplish the task. It will be seen that those with far advanced nephritis require 3 times as much water as the normals to prevent retention. All of this extra water is obtained at the expense of body water and must cause a dehydration of at least 1500 cc. daily.

TABLE 8.

Case Diagnosis	Concentrating ability specific gravity.	No. of cases.	Grams per 24 hours.	
			Urine water.	Urine solids.
Normal	1.029-1.032	8	456	32.95
Abnormal	1.025-1.029	4	594	34.94
Group A	1.020-1.025	7	713	41.22
No nephrotic edema	1.015-1.020	5	971	39.81
	1.010-1.015	4	1355	32.69
Abnormal—Group B	1.0203		247	13.82
Nephrotic edema .	1.0096		845	18.89

When edematous nephritics are subjected to these conditions a totally different response is obtained. The volume of the urine is small (in comparison with the specific gravity) and a marked retention of urinary solids takes place. The next table (Table 9) gives a summary of the water exchange in these different groups. It is seen that the non-edematous chronic nephritic loses about 4 times as much body water as the edematous nephritic; further, that edema unassociated with kidney disease does not prevent a large dehydration. These facts may be interpreted in either of two ways: (1) The kidneys of persons afflicted with the edematous type of nephritis hold back water and solids. (2) The water needed to form a large volume of urine does not reach the kidneys, because it is too firmly attached to the tissues throughout the body. A decision is easily reached by the simple expedient of causing these various groups of persons to drink a large amount of water. Table 10 shows the outcome of such an experiment. Of chief interest is the enormous increase in the volume of the urine displayed by the

TABLE 9.—WATER EXCHANGE—RENAL DISEASE.

Subject.	Available, grams.	Excreted, grams.	Dehydration, grams.
Normal	760	1724	963
Chronic nephritis, no edema	693	2840	2147
Chronic nephritis, massive edema	546	1053	507
Severe anemia, marked edema	769	2650	1881

TABLE 10.

Case diagnosis.	Part A, water restricted.		Part B, water as desired.	
	Grams per hour.		Grams per hour.	
	Urine water.	Urine solids.	Urine water.	Urine solids.
Normal	20.86	1.445	36.55	1.545
Chr. nephritis				
No. 30. With hypertension	75.16	1.375	205.10	1.572
No edema				
Chr. parench.				
No. 26. Nephritis	8.78	0.505	161.50	1.445
Edema marked				

edematous nephritic when much water is taken. And accompanying this response is the three-fold increase in excretion of urinary solids. Clearly such kidneys can excrete large amounts of water and solids when the water reaches them. Renal edema cannot therefore be attributed to impermeability of the kidneys.

Such evidence makes it clear that the kidneys of both types of chronic nephritics need more water than the normals to remove the same amount of waste. If sufficient water does not reach the diseased kidneys, retention will inevitably occur. Edema fluid is not available to the kidneys and should not be thought of as part of the supply of water. Hence it is just as important for edematous nephritics to ingest large amounts of water as it is for nephritics without edema to do so.

In order to demonstrate the value of furnishing a large amount of water to patients with renal disease, the following cases are presented:

CASE 1.—*Chronic Nephritis Without Edema.* This patient, aged 61, was a typical example of chronic nephritis with uremia. When admitted to the University Hospital, there were present drowsiness, twitchings, albumin, red cells and casts in the urine, and a blood non-protein nitrogen of 123 mg. per cent. The concentrating ability of the kidneys was 1.010 (specific gravity). At this concentration a minimal urine output of 2200 cc. is required for the excretion of the average amount of waste products. Therefore, it was concluded to force fluids to the extent necessary to obtain at least that urine volume. It was found that when he received 5000 to 8000 cc. of water daily, the desired output of urine was obtained. As long as the urine output was above 2500 cc. daily, the blood non-protein nitrogen decreased progressively. It fell from 150 mg. to 75 mg. per cent in 11 days. This is very striking when one considers that the renal damage was so severe that the patient succumbed in uremia a few days later. Even under these conditions the kidneys were able to reduce the blood non-protein-nitrogen when the water intake was sufficiently large.

CASE 2.—*Chronic Nephritis With Edema.* This patient was typical of that group of young individuals with chronic nephritis and massive edema of insidious onset. She had been a patient in the University Hospital on previous occasions. Each time she had had massive edema with ascites, marked albuminuria, casts and red blood cells in the urine. The blood non-protein nitrogen and blood pressure had always been normal. At the last admission the above findings were again present. The blood non-protein nitrogen was 40 mg. per cent and the blood pressure was systolic 164 and diastolic 112 mm. Hg. In spite of the edema, she was given 5000 to 6000 cc. of water daily. During a period of 30 days the patient's weight decreased from 51.0 to 38.4 kilos and the blood pressure dropped to systolic 124 and diastolic 74 mm. Hg. Since she had been receiving an adequate diet, the loss of 11.6 kilos (25.5 pounds) was due to loss of edema.

The above examples make it quite clear that patients with renal disease should always receive enough water so that the specific gravity of their urine is at all times well below the maximal gravity of which their kidneys are capable. It needs to be repeated that edema is not a contraindication to such therapy.

The physician encounters many patients whose kidneys are

normal but who are ingesting little or no fluid, or who are vomiting or having a watery diarrhea. May the failure to consider the amount of water at hand for renal function under such circumstances jeopardize the previously normal kidneys? Attention directed toward this point has afforded us evidence that even normal kidneys may be at a great disadvantage through lack of water.

The following records show how various degrees of renal damage may unwittingly be permitted to develop:

CASE 3.—This patient, aged 38, had suffered from attacks of severe headaches, drowsiness, and sensory disturbances of the extremities for 2 years. During this period he had had hypertension without albuminuria. On October 23, 1932, another severe headache developed, accompanied by an increasing drowsiness that ended in coma. The next day the patient was admitted to the University Hospital. The coma was obvious. In addition, perspiration was so marked that huge beads were visible on the body at all times. The respirations were deep and rapid. The fundi showed marked arteriosclerosis of the retinal vessels with retinal hemorrhages. Systolic blood pressure was 160 mm. Hg, and the diastolic 90. Up to October 26th the patient received no fluid other than that yielded by the oxidation of his own tissues. This amounted to about 500 cc. daily. During this period he voided about 500 cc. of urine daily. But as already made clear, he must have lost much water by evaporation from the skin (perspiration) and lungs (rapid respirations). The conditions permitted us to calculate that this amounted to about 2500 cc. daily. Accordingly, the 7000 to 8000 cc. lost from October 23d to 26th must have reduced the water normally present in his body to the extent of 7 to 10 per cent. On the morning of October 26th the urine contained 1 per cent of albumin, many casts and red blood cells, and the blood non-protein-nitrogen had risen to 75 mg. per cent. However, the specific gravity of the urine was 1.030 and this meant that the renal function was still normal. Accordingly, one could not attribute the retention to renal disease. It was, in fact, solely due to lack of water, for when the patient received 8000 cc. of water intravenously, there was a sharp fall of the blood non-protein nitrogen to 50 mg. per cent within 24 hours. He died on the 28th. Necropsy clearly indicated that the coma had been caused by cerebral hemorrhage. The kidneys revealed no gross nor microscopic abnormalities.

On the basis of these data it would seem that when the body is dehydrated to the extent of 7 per cent of its weight, there is only a small reserve of body water left. As a result, the water available to the kidneys is not sufficient for the excretion of the waste products in spite of their high concentrating ability. Furthermore, this amount of dehydration is enough to produce albuminuria, casts and red blood cells in the urine. But not enough renal damage has yet occurred to reduce significantly the concentrating ability of the kidneys or cause marked morphologic changes. Dehydration of this type is often overlooked by failing to consider those losses of water from the body other than the urine.

CASE 4.—This patient was a youth aged 17. It was known that his urine had been normal in the past and no urinary abnormalities were found when he was admitted to the University Hospital. The acute intestinal

obstruction that caused his admission was surgically relieved 4 hours after the onset. Following the operation there were persistent vomiting, watery diarrhea and drainage from a colostomy tube. In order to meet this loss of water the surgeons gave him about 3500 cc. of fluid daily. The convalescence seemed to be progressing satisfactorily. But on the 16th day he voided only 250 cc. of urine. It contained albumin, casts and red blood cells. The blood non-protein nitrogen was 57 mg. per cent, the blood pressure 160/90 and the patient was drowsy. When we compared the total loss of water from the body with the available water, it was found that he had been dehydrating himself to the extent of about 1000 cc. daily. This huge dehydration developed in spite of what superficially appeared to be a satisfactory supply of water. The effect here was so great that the previously normal kidneys were now able to reach a maximal concentration of only 1.010. This striking decrease in their functional ability was evidence of grave damage. At this point 8000 cc. of fluid were given the first day and 5000 cc. or more each subsequent day for about 2 weeks. As a result of this treatment, the blood non-protein-nitrogen and blood pressure returned to normal within 2 weeks. But the urine did not. Thus, the severe and prolonged dehydration had evidently caused so much renal damage that it took the kidneys several months to develop normal urine and concentrating ability.

The paramount importance of a sufficient supply of water is again demonstrated.

We hope that we have by now convinced you that the determination of the exchange of water is a powerful addition to our methods of investigating the nature of disease.

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THE BACTERIAL FLORA WITHIN THE STOMACH AND SMALL INTESTINE.

THE EFFECT OF EXPERIMENTAL ALTERATIONS OF ACID-BASE BALANCE AND OF THE AGE OF THE SUBJECT.

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THE mucosa of the gastro-intestinal tract is the covering of the splanchnic body surface. The physician is accustomed to think of the alimentary tract as a digesting and absorbing organ. The hydrolysis of carbohydrates, fats and proteins takes place within the lumen of this tract, hence outside of the body. Bacteria are present within

the lumen of the gastro-intestinal tract. This is a unique body surface. It is a mucous membrane and has densely populated bacterial communities residing in direct contact with it. We wish to consider this body surface from the bacteriologic standpoint.

The bacterial flora of the normal stomach contains a few acid-resisting types. The flora of the duodenum and upper half of the jejunum contain a scanty enterococcal type; few if any Gram-negative bacilli are present in the upper segments in normal individuals during the postdigestive state. The contents of the ileum has a rich and varied bacterial flora, similar to that present in the large intestine. Although the lumen of this tract is a continuous tube, the bacterial flora varies considerably within certain levels. The digesting and absorbing duodenum and jejunum contain few bacteria. The bacterial flora of the various levels of the small intestine can be controlled under certain experimental conditions. Arnold¹ reviewed some of the results obtained in this laboratory upon the variations in the endogenous bacterial flora in relation to diet and climate.

There is a relationship between the endogenous bacterial flora and the acid-base equilibrium of the contents of the small intestine. The contents of the duodenum and upper half of the jejunum has a hydrogen-ion concentration of approximately pH 5 to 6.5 during the resting postdigestive state. This is biochemically the most active zone of the enteric tract. This level can under normal conditions rigidly control its endogenous bacterial flora. Exogenous flora swallowed by mouth rapidly disappear as viable entities from the contents of this part of the enteric tract. Our results have led us to believe that the acid-base balance mentioned above is an index of a normal gastro-intestinal tract. The hydrogen-ion concentration of pH 5 to 6.5 is not detrimental to the growth of bacteria in *in vitro* experiments. When the mucosa of the duodenum and jejunum is normal, this membrane has the power of controlling the type of bacterial life residing upon its surface.

During the period of the specific dynamic action after a protein meal, the acid-base equilibrium of the small intestine is not disturbed, but the bacterial flora of the large intestine ascends up into the small intestine. During the period of specific dynamic action there is an interference with the self-disinfecting power of the small intestine. The same reaction takes place in a warm and humid room, it is also present after a mild form of foreign protein intoxication.¹

We wish to show in this communication that the wall of the intestinal tract is not impermeable to bacteria, but that the bacterial flora within the lumen of the upper half of the small intestine can pass through the wall, and it is the function of the liver and mesentery lymph glands to remove from the splanchnic circulation such bacteria as gain entrance into the body through the intestinal mucosa.

We wish to show that the gall bladder plays a rôle in this bacterial cycle. The diminution in gastric acid secretion with advancing age over 40, the changes in the types of bacterial life within the lumen of the small intestine, can well be associated with some of the dysfunctions observed in the organs within the splanchnic area so common in the age group over 40.

Experiments. *Methods of Changing the Distribution of the Intestinal Bacterial Flora.* Certain surgical procedures have been carried out upon the gastro-intestinal tract of dogs so as to fix given portions of the small intestine beneath the skin. Material can be aspirated for chemical and bacteriologic studies, and the injection of desired bacteria or chemicals into the lumen of the tract can be carried out at any desired levels.² Another method has been to prepare non-leaking gastric and cecal fistulæ. The time, rate and concentration of bacteria and other substances can be followed from the stomach to the large intestine. We have studied the bacterial flora of the small intestine by combining these two methods upon the same group of animals. A third experimental method has been to sacrifice the animal after a given period of time following oral administration of the test bacteria. General and local anesthetics have been used to expose the small intestine and material injected directly into the lumen. Such animals were killed after a certain period of time.

The relationship between the acid-base equilibrium and the bacterial flora of the duodenum was reported by Arnold and Brody.³ When the reaction is changed by injecting alkalin-buffered phosphates there appears within a short period of time a coli-aërogenes bacterial flora which is common under normal conditions to the large intestine. Animals placed in warm and humid temperature rooms show a change in the distribution of the enteric flora.⁴ The fecal type of flora of the lower intestinal tract was found in the lumen of the duodenum during the period of fever following foreign protein injections. The duodenal flora returned to normal as soon as the animal recovered.³ The gastro-intestinal irritant in certain Salmonella food poisonings causes a change in the distribution of the endogenous bacterial flora.⁵

Associated with the ascension or extension of the flora from the lower segments of the intestinal tract into the duodenum and upper jejunum is a loss of the power to destroy foreign or exogenous bacteria ingested by mouth. The body surface covered by the mucosa of the upper half of the small intestine is a specialized absorbing area. Ferments hydrolyze proteins, sugars and fats within the lumen of this part of the digestive tract and absorption proceeds rapidly. This part of the alimentary canal is relatively free of bacteria. The undifferentiated enterococcus type composes the endogenous flora and these are present in relatively small numbers.

Furby⁶ has shown that manipulation of the small intestine in the

anesthetized animal causes a loss of the power to control the bacterial flora in contact with the mucosa. Kaufman⁷ has shown that the oral administration of saponin in mice causes the sudden appearance of a coli-aërogenes type of flora in the stomach. Associated with this was a change in the acid-base equilibrium. Nedzel⁸ has extended these observations to dogs. In addition to confirming Kaufman, this worker showed that there was an extensive invasion of the splanchnic organs with *B. coli* at the time of the alterations in the bacterial flora and acid-base equilibrium within the lumen of the stomach and upper part of the small intestine. Nedzel⁸ has gone farther and shown that when the stomach is isolated from the small intestine in acute experiments and saponin is injected into the lumen, *B. coli* appears in viable form within a few minutes. Before the administration of the saponin repeated cultures from the stomach did not show the presence of any members of the coli-aërogenes group. This would exclude ascension of *B. coli* from the distal segments of the enteric tract. Seidmon⁹ has found a change in the bacterial flora and also in the acid-base equilibrium of the small intestine in avitaminosis. Nedzel and Arnold¹⁰ showed a cyclic circulation of bacteria from the lumen of the intestinal tract into the splanchnic circulation. The bile was shown to contain some of the intestinal test bacteria and in this way these microorganisms are returned to the lumen of the intestinal tract. These workers used fresh egg white as a medium to increase the rate of passage of bacteria through the wall of the intestine. At least a larger number of viable bacteria can be demonstrated to be present in the liver and mesenteric lymph node after the application of fresh egg white to the mucosa of the duodenum and jejunum.

Finder^{11,12} showed that bile and also fresh egg white administered by mouth cause a decrease in the acid secretion of the stomach for a short period after ingestion. Finder and also Simon¹³ have used bile as a vehicle to convey an antigen through the stomach and thereby obtain the optimum conditions for intestinal absorption. The inhibition of acid secretion by the stomach is accompanied by shifting of the acid-base balance of the upper part of the small intestine toward the alkaline side. In our experience this is associated with increased permeability of the intestinal tract.¹

The wall of the intestinal tract does not seem to be an impermeable membrane. Fisher¹⁴ has shown that yeast can be demonstrated in the liver and mesenteric lymph nodes of animals after oral ingestion. Yeast as well as bacteria are rapidly destroyed within the body after passing through the mucosa of the intestinal tract. The time interval of examination must be less than 3 hours; we have found more viable ingested bacteria and yeast in the organs of the splanchnic region $\frac{1}{2}$ hour after ingestion than at any other time interval.

The alterations in the equilibrium of the vegetative controlling apparatus of the body have been produced in all of the methods

we have employed in studying the bacterial flora and acid-base balance of the lumen of the intestinal tract as well as the permeability of the wall of this tract. This was dealt with in detail in connection with the demonstration of viable bacteria in the thoracic duct lymph after intraduodenal injection.¹ The *in vitro* acidity or alkalinity of the duodenum, at the time of disappearance or prolonged viability of bacteria within the lumen of this organ, has not proved to be detrimental to bacteria. We have interpreted the acid-base balance and the type of bacterial flora within the lumen of the small intestine as dependent upon the functional status of the mucosa. The splanchnic body surface or the mucosa of the alimentary tract possesses the power in the normally reacting animal of controlling the viable bacterial flora residing within its lumen and contact with the mucosa of the upper portion of this tract. There is a delicate adjustment of the acid-base equilibrium within the lumen of the cephalad half of the small intestine.

The bactericidal power of the acidity of the gastric juice has been studied by Johnson and Arnold¹⁵ in *in vivo* experiments. Dogs with non-leaking gastric fistula were used for these experiments. Bacteria were introduced into the stomach through the fistula; specimens were removed at frequent time intervals. Bacteriologic cultures and chemical titrations of the relative acidity were determined. A stomach containing free acid was found to destroy the viability of the bacteria. When no free acid was present, the bacteria remained viable. These observations substantiate the accepted theory of the bactericidal action of the free hydrogen-ion in the gastric juice. The acid-secreting stomach does not seem actually to destroy bacteria. The same bacteria reappear in the stomach as soon as an acid deficit occurs. We have substantiated the old observation that many stainable bacteria are present in the contents of the free acid stomach although none grow on bacteriologic media. But if time is allowed for the disappearance of the free acid, some of the bacteria grow on media. Bacteria were introduced into a fasting acid-deficit stomach. Specimens removed at frequent intervals showed a large number of viable bacteria. The animal was allowed to smell meat. The free acidity following this method of stimulation of gastric juice was associated with non-viable or culturally sterile gastric contents. After this period of stimulation had passed and an acid-deficit was again present, the test bacteria introduced at the beginning of the experiment reappeared in large numbers. In all of our experiments there was a correlation between the acid-base balance of the contents of the lumen of the stomach and the viable bacteria. When free hydrogen-ions appear, the bacteria within the contents are non-viable. Bacteria are viable when an acid-deficit condition exists. Two waves of free acidity with alternating acid-deficit periods over a time interval of 6 hours have been frequently observed. The subcultures of the contents are sterile

during periods of free acidity and the cultures are overgrown with the test bacteria during periods of acid deficit. Johnson and Arnold removed specimens from the free-acid stomach, after introducing bacteria, and neutralized this material *in vitro*. Subcultures made from the original acid-reacting gastric contents and the neutralized specimens were sterile. When bacteria are viable in an acid-deficit stomach and some of the contents is removed and acidified *in vitro*, the subcultures become sterile on the same media. The bactericidal action of the free hydrogen-ion can be demonstrated in *in vitro* experiment.

Johnson and Arnold investigated this phenomenon of viability of bacteria within the gastric lumen in the following manner: The gastric response of each of our experimental animals was well known after working for 15 months with them. Bacteria suspended in saline were introduced into the free-acid secreting stomach of a dog. The total contents was removed as soon as it was completely acidified. Bacterial cultures were made. This material was next neutralized with sodium hydroxid solution. Cultures were again placed upon agar and in broth. The neutral content was now introduced in an acid-deficit stomach of a second dog. Of the original test bacteria 200,000 per cc. would appear in a viable state within 5 minutes in the second dog. Both of the free-acid reacting material from the first dog's stomach and this same specimen after *in vitro* neutralization was sterile when cultured in the same amounts upon the same media. If the same experiment is repeated, but the neutralized gastric contents of the first dog is passed through a Berkefeld filter, no test bacteria can be demonstrated in the gastric lumen of the acid-deficit second dog. We are not dealing with a filter-passing substance as determined by this technique. Nedzel¹⁶ performed acute experiments upon dogs under nembutal anesthesia. The stomach was isolated and Johnson's findings were substantiated. Intracutaneous injections of histamin were used to produce acid secretion. Alkaline phosphate was introduced into the gastric lumen to neutralize the acidity. The stomach was separated from the duodenum and regurgitation of intestinal contents into the gastric lumen was excluded. Test bacteria are non-viable when transferred from the stomach containing free acid to growth promoting media. But if alkaline phosphate is now introduced into the gastric contents to neutralize the free acid, the test bacteria originally introduced become viable and grow when placed upon nutrient media.

The control of the bacterial flora within the lumen of the stomach seems to be a complicated mechanism. The acid secreted by the mucosa does not seem to be bactericidal within the lumen of this organ. Another interesting observation was recorded by Ryan.¹⁷ This worker used a modification of Hauduroy's¹⁸ technique of a series transfer of bacterial cultures. The postdigestive empty stomach and duodenum were shown to be free of any bacterial

growth when surface swabs were smeared well over agar media and incubated 48 hours. But if this apparently sterile agar surface is washed off with a little sterile saline and transferred to a second agar petri dish, smeared well over the surface and again incubated, no visible growth occurs on the surface. Ryan repeated this technique for several transfers. After the 5th to the 20th transfer a growth would appear on the agar surface. There have been controls with only saline used for the original inoculation and these transfers have remained sterile for over 50 transfers. The mucosa of the stomach and duodenum are not sterile if the technique used by Ryan is employed. This same technique is now being applied to a variety of apparently sterile materials.

Andrews and his coworkers^{19,20} have shown that bacteria already present locally in tissue can be made to multiply when the area is damaged in certain ways. It is interesting to note that the *B. welchii* was the organism of greatest concern to Andrews. This is the spore-bearing type of intestinal bacteria. The work in this laboratory has dealt mainly with the bacteriology of the upper part of the small intestine. Fisher²¹ has shown that yeasts are absorbed from the large intestine in dogs. A particularly interesting part of Fisher's experiments dealt with the increase in the viable yeast cultured from the internal organs after rectal injection of yeast and oral administration of egg white. Shuger²² showed that after the introduction of sterile saline by rectum to dogs, *B. coli* could be cultivated from the mesenteric lymph node, liver, spleen and lung of 75 to 100 per cent of the animals within 15 minutes. The viable bacteria decrease rapidly and are not demonstrable after 45 minutes. Certain exogenous bacteria were suspended in saline and administered by rectum and were cultivated from certain internal organs shortly after intrarectal injection—*B. prodigiosus*, *B. murii* and *B. welchii* were the bacteria used by Shuger. Reith and Squier²³ have shown that 293 healthy persons gave 113 positive blood cultures. Some of these had demonstrable focal infections but could be classed in general as healthy persons. It is entirely possible that there is a physiologic bacteriemia in the portal blood returning from the gastro-intestinal tract. The types of bacteria composing the endogenous flora of the intestinal tract (enterococci, *Streptococcus fecalis*, coli-aërogenes, aciduric bacteria) are non-antigenic. This may well be due to the early and persistent contact these bacteria have with the body cells. They normally pass into the portal system and also in the lymph system and are usually phagocytized within the splanchnic area.

The physician seldom considers the lining mucosa of this tract as a body surface. When considered from this standpoint the contents of the lumen of the enteric canal becomes important. The acid-base equilibrium of the material within the lumen of the gastro-intestinal tract as well as the variety and density of the bacterial

communities residing upon this body surface are of importance in health and disease. The gastro-intestinal tract must be considered from a new standpoint or rather the present viewpoint should be extended to include certain newer bacteriologic information. The changes in the functional status of the gastro-intestinal tract during the last third of life are well known. There are changes in the response of the gastric mucosa to physiologic stimuli as recorded by a variety of reports upon gastric aspiration of older people. Van der Ries²⁴ reviewed the literature upon the relationship between the acid gastric secretion and the bacterial flora of the small intestine. Diminished concentration of acid in the stomach was associated with an increase in the number and also an increase in the variety of bacteria within the lumen of the small intestine below the pylorus. Ricen, Sears and Downing²⁵ found only a few aciduric bacteria in the duodenum of their normal subjects. They found a mixed and rich flora in this region in achlorhydric patients. Bloomfield and Keefer^{26,27} concluded that as people grow older they tend to secrete a less acid gastric juice. Davies and James²⁸ report upon the gastric analysis of 100 normal healthy people over 60 years of age; achlorhydria was present in 32 per cent, hypochlorhydria in 12 per cent, normal in 43 per cent and high secretion in 13 per cent. Poeschel²⁹ found anacidity so prevalent in older people that he cautions against placing too much weight on this test in gastric carcinoma diagnosis. MacLean and Griffiths³⁰ and Norris³¹ have emphasized the automatic and self-limiting process of gastric acid secretion. Klinge³² considers the gastric mucosa to have a bacterial killing power independent of its hydrochloric acid secretion. Mueller and Petersen³³ called attention to the fact that gastric secretion is associated with hyperemia, dilation of the stomach and during this physiologically active phase of the stomach and other glands in the splanchnic area there is a relative decrease in the functional status of the skin and underlying muscle systems. They bring up the autonomic regulation of gastric secretion as a correlated function of the vegetative nervous system. Mettier³⁴ has shown the dependence of the acid-base equilibrium of the upper end of the small intestine upon the acid content of the lumen of the stomach. Stuart³⁵ has shown that there are two toxic substances in *B. coli* cultures. The Berkefeld filtrate of a 48-hour *B. coli* culture contains a heat-labile neurotropic toxic substance. The Berkefeld filtrate of a 14-day-old broth culture of *B. coli* contains a heat-stable enterotropic toxic substance. The oral administration of 2.5 cc. per kilo to rabbits every 3d day for 5 weeks of this enterotropic toxic *B. coli* filtrate causes diarrhea after 3 to 4 weeks, loss of weight and death after 8 to 12 weeks. The rabbits were young and fed carrots and cabbage daily. The controls gained weight in the normal manner. Plantenga³⁶ carried out a similar experiment upon young calves and observed similar reactions. It is then pos-

sible to cause a chronic diarrhea in certain animals by continuous oral administration of by-products of growth of *B. coli*. Stuart isolated the coli strains used in his experiments from rabbits, he was using the endogenous coli for this animal. Moro's^{37,38} ideas upon the endogenous source of summer diarrhea in infants is an example of the type of reaction under discussion. Moro found a rich *B. coli* flora in the duodenum of infants with dyspepsia and fever associated with diarrhea, and could not find any abnormal bacteria in the feces. He regarded the *B. coli* in the duodenum, where they are normally seldom found and if so only in small numbers, as the source of the toxic material causing the symptom complex in these infants. Catel³⁹ can be cited as doing a type of work along the same line from Bessau's Clinic. The various fatty acids produced from milk by bacteria found in the upper enteric levels have been investigated by this group of workers to explain the systemic intoxication of infants. The author's conception of this problem has been published elsewhere.⁴⁰

The changes in the acid-base balance and in the endogenous bacterial flora of the upper part of the small intestine during advancing ages over 40 bring up a question of gradual alterations in the normal equilibrium with the development of a chronic or persistent disturbance within the lumen of the duodenum and upper jejunum. In our experimental work we have been led to believe that more bacteria can be demonstrated to be viable in the splanchnic organs if we can change the gastro-intestinal tract to approximate that found in the hypogastric functioning types so often encountered in older people.

Summary. The mucosa of the gastro-intestinal tract has been considered as a body surface covering layer. The acid-base balance and the bacterial flora of the stomach, duodenum and jejunum are associated together. Alterations in the acid-base balance toward the alkalin side are associated with the appearance of a coli-aërogenes type of flora in the duodenum and even in the stomach. Evidence has been presented to show that in addition to ascension of this flora, the same types can appear within the lumen after the continuity of the tract has been interrupted. Attention is called to the importance of the bacterial flora in contact with this splanchnic body surface in the older age groups. This may be a significant factor in some of the degenerative or retrogressive diseases of later life. The action of the acid gastric juice upon bacteria has been shown to be more bacteriostatic than bactericidal in nature. These findings are significant from an epidemiologic standpoint.

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STANDARDS FOR MAXIMUM RETICULOCYTE VALUES FOLLOWING VENTRICULIN AND INTRAVENOUS LIVER EXTRACT THERAPY IN PERNICIOUS ANEMIA.

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EARLY remission in pernicious anemia is accompanied by an increase in reticulated red blood cells. The degree of reticulocyte response was shown by Minot and his associates to be uniform and

predictable in relation to the erythrocyte count before treatment with liver.¹ Subsequently the daily determination of the reticulocyte percentage until a maximum value is obtained has been the generally accepted means of assaying the potency of other modes of treatment proposed for this condition.

The formula: $R = \frac{0.73 - 0.2 E_o}{0.73 + 0.8 E_o}$, obtained by combining the

two equations of Minot and Cohn: $E_p R = \frac{E_o R}{1 - R} = 0.73 - 0.2 E_o$,

in which E_o represents the erythrocyte count at the beginning of treatment, E_p the erythrocyte count at the time of the maximum reticulocyte response, and R the maximum percentage of reticulocytes, was found by Riddle in this laboratory to be reasonably accurate in predicting the magnitude of the reticulocyte percentage response in cases treated with the usual dose of liver extract orally.²

Observations on patients undergoing treatment with desiccated stomach derived from 265 gm. of original tissue indicated that a definitely greater response could be expected from this form of therapy than from the oral administration of liver extract No. 343, derived from 600 gm. of fresh liver.³ With the assistance of Dr. W. D. Baten, of the mathematics department of the University of Michigan, a formula has been devised which expresses the mathematical relationship between the initial erythrocyte count and the maximum reticulocyte percentage, the data employed being obtained from the study of 43 cases of pernicious anemia each receiving 40 gm. of desiccated stomach daily.

$$R = \frac{91.6 - 25.9 E_o}{1 + .57 E_o}$$

A similar formula has been prepared from the initial erythrocyte count and the maximum reticulocyte percentage values obtained from 39 cases of pernicious anemia each treated with a single dose of intravenous liver extract made from 100 gm. of liver. This form of therapy leads to a reticulocyte response of considerably greater magnitude than is secured from the oral administration of liver, liver extract, or desiccated stomach.

$$R = \frac{93.7 - 24 E_o}{1 + .47 E_o}$$

Curves are presented which express the correlation of the initial erythrocyte counts and maximum reticulocyte percentage responses obtained with oral liver extract (Riddle), desiccated stomach and intravenous liver extract therapy.

Tables are given of the expected maximum reticulocyte percentage response calculated by the above formulæ from various initial erythrocyte counts.

THE EXPECTED MAXIMUM RETICULOCYTE PERCENTAGE AFTER DIFFERENT MODES OF TREATMENT IN PERNICIOUS ANEMIA, WITH VARIOUS RED BLOOD CELL COUNTS.

Oral Liver Extract
(From 600 grams of liver daily).

$$R = \frac{0.73 - 2 E_o}{0.73 + 0.8 E_o}$$

Desiccated Stomach
(From 265 grams of stomach daily).

$$R = \frac{91.6 - 25.9 E_o}{1 + .57 E_o}$$

Single Intravenous Dose of Liver Extract
(From 100 grams of liver).

$$R = \frac{93.7 - 24 E_o}{1 + .47 E_o}$$

Eo	R
0.4 =	61.9
0.5 =	55.7
0.6 =	50.4
0.7 =	45.7
0.8 =	41.6
0.9 =	38.0
1.0 =	34.6
1.1 =	31.7
1.2 =	29.0
1.3 =	26.5
1.4 =	24.3
1.5 =	22.3
1.6 =	20.4
1.7 =	18.7
1.8 =	17.1
1.9 =	15.6
2.0 =	14.1
2.1 =	12.9
2.2 =	11.6
2.3 =	10.5
2.4 =	9.4
2.5 =	8.4
2.6 =	7.5
2.7 =	6.6
2.8 =	5.7
2.9 =	4.9
3.0 =	4.1
3.1 =	3.4
3.2 =	2.7
3.3 =	2.1
3.4 =	1.5
3.5 =	0.9

Eo	R
0.4 =	66.1
0.5 =	61.2
0.6 =	56.6
0.7 =	52.5
0.8 =	48.7
0.9 =	45.1
1.0 =	41.8
1.1 =	38.8
1.2 =	36.0
1.3 =	33.2
1.4 =	30.8
1.5 =	28.4
1.6 =	26.2
1.7 =	24.2
1.8 =	22.2
1.9 =	20.3
2.0 =	18.6
2.1 =	16.9
2.2 =	15.4
2.3 =	13.9
2.4 =	12.4
2.5 =	11.1
2.6 =	9.8
2.7 =	8.5
2.8 =	7.3
2.9 =	6.2
3.0 =	5.1
3.1 =	4.1
3.2 =	3.1
3.3 =	2.2
3.4 =	1.2
3.5 =	0.3

Eo	R
0.4 =	70.8
0.5 =	66.1
0.6 =	61.8
0.7 =	57.8
0.8 =	54.1
0.9 =	50.6
1.0 =	47.4
1.1 =	44.3
1.2 =	41.5
1.3 =	38.8
1.4 =	36.2
1.5 =	33.8
1.6 =	31.5
1.7 =	29.4
1.8 =	27.3
1.9 =	25.4
2.0 =	23.5
2.1 =	21.8
2.2 =	20.1
2.3 =	18.5
2.4 =	16.9
2.5 =	15.5
2.6 =	14.1
2.7 =	12.7
2.8 =	11.4
2.9 =	10.2
3.0 =	9.0
3.1 =	7.8
3.2 =	6.7
3.3 =	5.3
3.4 =	4.6
3.5 =	3.6

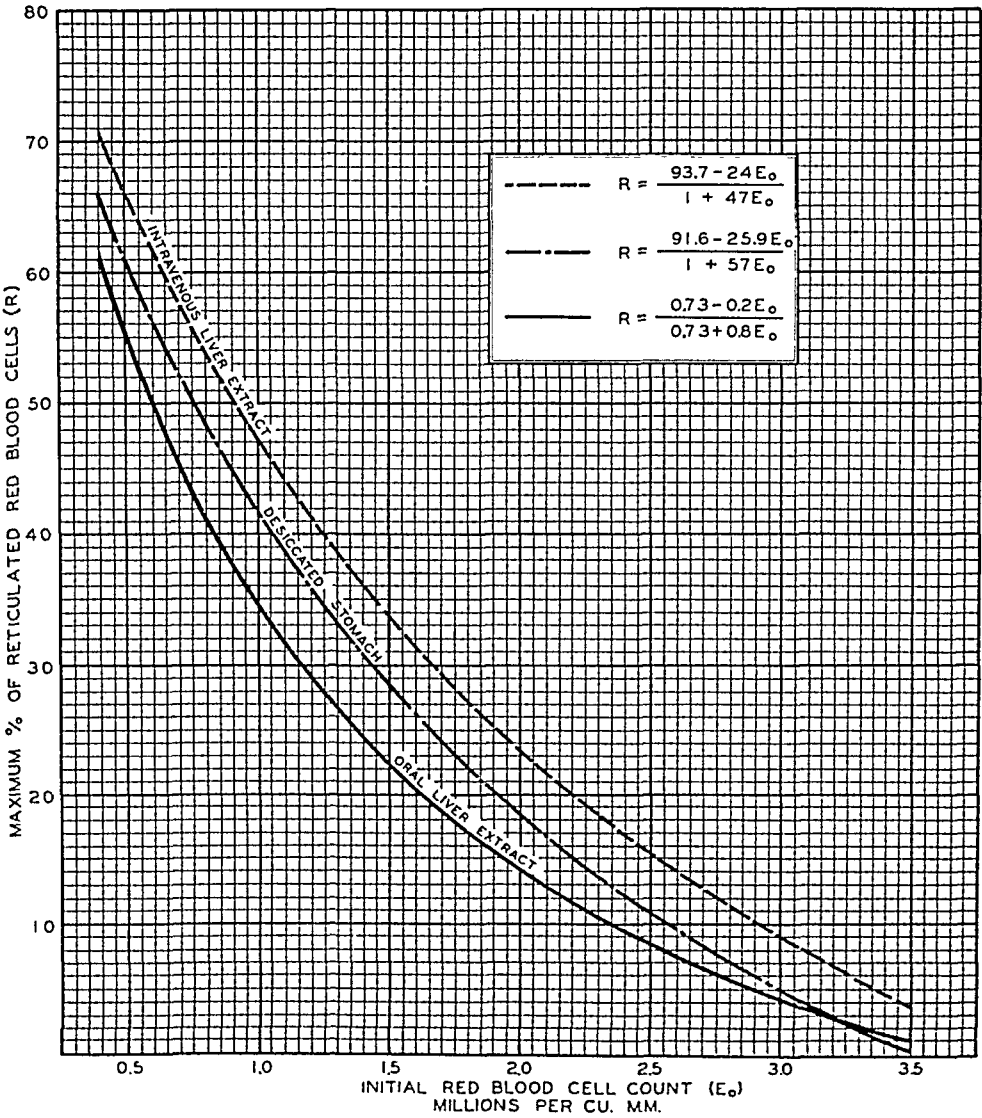
Eo = Initial red blood cell count in millions per c.mm.

R = Maximum reticulocyte percentage.

It should be borne in mind that the error in counting red blood cells when their number is within normal limits is about 5 per cent. that with lower counts the error may be greater. Furthermore, as the number of reticulocytes in the peripheral blood is constantly fluctuating, it is unlikely that the maximum value will be obtained when only one count is made daily. Consequently strict agreement between the data of the tables and observations on individual patients is not to be expected.

The significance of the different degrees of response on the part of the reticulocytes probably lies in the rate at which the potent material reaches the bone marrow, and not on the total amount of potent material administered to the patient. Whereas a maximum

reticulocyte response may be obtained with an extract derived from 100 gm. of liver given intravenously, at least 30 times this amount is required *via* the oral route. This suggests either incomplete absorption from the gastro-intestinal tract or partial destruction by digestion. The substance normally present in the stomach



Correlation of maximum reticulocyte values and initial blood cell counts during treatment with oral liver extract and Ventriculin (daily) and intravenous liver extract (single injection derived from 100 grams of liver).

which is believed to play an essential part in the formation of red blood cells is associated with digestion and its ultimate effect upon the bone marrow is dependent upon absorption by the gastro-intestinal mucosa. The active principles of stomach and liver differ in their physical and chemical properties. In the normal

individual it has been shown that the liver is a storage depot from which the hematopoietic substance may be transported by the blood to the bone marrow as required.⁴ In this process gastro-intestinal absorption plays no part. This difference in the mode of utilization by the normal individual of the blood-forming substances present in his stomach and liver offers a possible explanation of the superiority, in pernicious anemia, of the oral administration of stomach to that of liver in smaller dosage per gram of original tissue. On the other hand, liver extract intravenously approximates more closely the normal method by which a substance stored in the liver would be supplied to the rest of the body. The tables of normal "reticulocyte response" may be used as standards in evaluating the potency of liver or stomach tissue preparations. A maximum reticulocyte percentage significantly below these percentages when corresponding dosages have been used in a patient with true pernicious anemia suggests (a) inadequate potency, (b) an infection preventing a proper response, (c) incomplete absorption, (d) arteriosclerosis.⁵

Conclusion. A comparison is drawn between reticulocyte response in pernicious anemia induced by customary doses of oral liver extract, desiccated stomach (Ventriculin) and intravenous liver extract. It is suggested that the effectiveness of these modes of treatment depends upon the amount of potent material which becomes available to the bone marrow.

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THE EFFECT OF EXERCISE ON THE LEUKOCYTE COUNT IN PULMONARY TUBERCULOSIS.

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REPORTS dealing with the leukocytic picture in pulmonary tuberculosis usually stress the importance of taking the counts during morning hours and during the same hour of the day for the same

patient on successive counts. The state of the patient, especially with reference to rest and posture before and while the count is taken, was given little consideration. The investigations of Garrey and Butler^{1,2,3,4} show how alterations in the physiologic state of the normal individual may result in definite and, at times, marked changes in the leukocyte count. These investigators have found that when a normal individual is in a state of complete relaxation resting in a recumbent position, the leukocyte count falls rapidly and progressively until after a sufficient time, usually less than 1 hour, the count will reach a minimum which for most human individuals lies between 5000 and 6000 leukocytes per c.mm. of blood. This level they have designated "basal level." For most individuals pursuing the ordinary routine work of a medical school laboratory the leukocytes averaged around 9000. This they have designated "activity level." They also state that under severe physical effort the count may reach very high levels and that nervous and psychic factors may also raise the leukocyte count. The "basal" count in a given individual was found by these authors to be constant from day to day. They did note, however, that there was a slight increase in the "basal level" in the late hours of the day. The rise in the leukocyte count following alterations in the physiologic state of the individual is attributed by these investigators to vasomotor changes which result in the liberation of leukocytes trapped in unused capillaries.

Since February, 1932, a series of patients with pulmonary tuberculosis on the author's service was followed with frequent total and differential leukocyte counts; over 1000 counts were made and since June, 1932, following the lead of Garrey and Butler, all the counts were made under "basal" conditions. In a few instances leukocyte counts were also made after a few minutes' walk, and when the results of the "basal" and "activity" counts were compared, it was noticed that the variations were marked in some cases and indifferent in others. It was, therefore, thought that it might be of interest to note the effect of exercise on the leukocytic picture in a larger group of tuberculous individuals.

Method and Results. In a group of 50 patients with pulmonary tuberculosis one "basal" and one "activity" count were made. For the "basal" count it was required that the patient be in bed and at rest for at least 1 hour before the count was taken. The patient was not allowed to read, listen to the radio, or engage in conversation with room-mates. The patient remained in the recumbent posture while the count was taken. For the "activity" count the patient walked to the laboratory (this department is located in the same building where the patients are housed). In some instances the patient was brought to the laboratory in a wheel chair. The activity count was taken while the patient was in a sitting position. The time that elapsed between the basal and

activity counts varied between 3 and 15 minutes. All counts were taken between 9 and 10 o'clock in the morning. In all counts certified pipettes and counting chambers were used. The average of four large squares was taken for the total count. For the differential counts (Wright's blood stain), 200 cells were counted for each smear—polymorphonuclears, lymphocytes, monocytes, eosinophils, and basophils. Since the significance of the eosinophils and the basophils in the tuberculous process is still an unsettled problem, these two types of cells will not be included here. The author has done all the differential counts and the total counts were done by a well trained technician.

No definite relationship could be established between the extent and activity of the lesion and the changes in the leukocyte count due to exercise. The time interval between the basal and activity counts likewise did not seem to definitely influence the activity counts.

The activity counts were increased in 38 cases and decreased in 12 cases. Out of the first group, 19 cases showed increases of less than 2000 cells. In 18 cases, the increases ranged between 2100 and 6800 cells and in 1 case the activity count showed a gain of 16,900 cells. In the latter instance the patient walked down from the third to the ground floor while on his way to the laboratory instead of using the elevator as he was instructed to do (this patient has been on all day bed rest treatment since October, 1931, and this was his first venture in walking down three flights of stairs).

Of the second group, 8 cases showed decreases ranging from 200 to 1950 cells and in 4 cases the decreases ranged between 2500 and 5100 cells.

Variations in the differential counts occurred in cases with increased as well as in those with decreased total activity counts. All cell types were affected and variations exceeding 100 per cent were noted in a considerable number of cases. The monocyte-lymphocyte ratio showed striking changes in some instances. (Table 1.)

Comment. Garrey and Butler, in their observations on normal individuals, found that a change from recumbency to standing posture causes an immediate rise in the cell count and the activity level is reached in less than 2 minutes. A drop in the cell count following exercise in some of the cases in this study was, therefore, a rather unexpected finding. It is noteworthy, however, that 6 patients out of the 12 who showed decreases in their activity counts, unlike the other 44 patients in the series, were unaccustomed to this procedure. Three others in the group were of the high-strung, nervous type, and 1 patient, although he had been having repeated basal counts for several months, was nevertheless still skeptical about the need of staying in bed at rest for a whole hour before a blood count is taken. There is, therefore, the possibility that these patients were under a certain degree of nervous tension while they

were awaiting their basal counts. This might have increased their attempted basal counts to an extent sufficient to overbalance the effect of exercise on their second blood counts.

TABLE 1.—DATA FOR BASAL AND ACTIVITY LEUKOCYTE COUNTS IN 50 CASES OF PULMONARY TUBERCULOSIS. (*Counts Expressed in Thousands.*)

Case.	Basal leukocyte counts.					Activity leukocyte counts.				
	Total white cell counts.	Polymorpho-nuclear leukocytes.	Lymphocytes.	Monocytes.	Monocyte-Lymphocyte Ratio.	Total white cell counts.	Polymorpho-nuclear leukocytes.	Lymphocytes.	Monocytes.	Monocyte-Lymphocyte Ratio.
1	9.3	7.0	1.1	1.01	0.95	26.2	16.6	6.3	2.9	.45
2	6.4	4.0	1.5	0.67	0.43	13.2	8.3	3.0	1.8	0.57
3	8.1	5.5	2.2	0.35	0.16	12.7	7.6	3.7	0.64	0.17
4	7.4	5.0	1.8	0.40	0.22	11.5	7.2	3.1	0.98	0.31
5	9.4	6.2	2.2	0.84	0.37	13.3	9.0	3.0	1.2	0.4
6	6.5	4.7	1.3	0.39	0.29	10.1	6.5	2.5	0.9	0.35
7	6.5	3.9	1.8	0.65	0.37	9.8	5.4	3.4	0.83	0.24
8	17.6	13.7	2.5	1.32	0.53	20.8	15.1	3.5	1.98	0.55
9	7.2	4.8	1.5	0.72	0.47	10.1	6.9	2.1	1.02	0.48
10	9.9	6.6	2.2	0.84	0.37	12.8	9.2	2.4	0.7	0.28
11	9.2	5.3	2.4	1.01	0.41	12.1	6.4	4.4	0.9	0.2
12	9.3	6.4	1.7	1.16	0.69	12.2	8.1	2.3	1.33	0.57
13	6.6	5.6	0.6	0.26	0.42	9.3	7.3	1.2	0.79	0.65
14	10.1	7.3	1.6	1.00	0.64	12.8	9.8	2.2	0.7	0.31
15	9.2	6.0	2.0	1.01	0.51	11.9	9.0	1.8	0.65	0.35
16	7.4	4.6	2.0	0.4	0.2	9.9	6.5	2.8	0.49	0.17
17	8.2	5.3	2.2	0.61	0.28	10.5	5.4	4.0	1.1	0.27
18	7.5	5.7	1.0	0.48	0.46	9.7	6.8	1.5	1.25	0.83
19	15.3	10.2	3.0	1.75	0.58	17.4	11.6	3.5	1.82	0.52
20	4.7	2.4	1.5	0.65	0.44	6.6	3.2	2.0	1.02	0.51
21	7.5	6.0	1.1	0.34	0.32	9.4	7.2	1.5	0.42	0.27
22	8.4	5.7	1.7	0.79	0.47	10.0	6.9	2.0	1.1	0.55
23	7.9	5.0	2.0	0.67	0.32	9.4	5.5	3.0	0.85	0.28
24	5.5	3.7	1.3	0.41	0.32	7.0	4.2	2.1	0.46	0.21
25	5.8	3.5	1.6	0.64	0.4	7.3	4.4	2.1	0.73	0.35
26	6.9	4.4	1.8	0.52	0.28	8.4	5.4	2.0	0.88	0.43
27	11.8	8.6	2.1	0.77	0.36	13.1	9.6	2.5	0.72	0.28
28	6.6	3.7	1.8	0.73	0.39	7.5	3.9	2.7	0.68	0.25
29	8.4	6.1	1.4	0.84	0.6	9.2	6.5	1.9	0.64	0.33
30	7.1	4.9	1.5	0.35	0.23	7.8	4.4	2.7	0.43	0.15
31	7.3	4.1	2.6	0.58	0.22	8.0	4.3	3.1	0.52	0.16
32	9.0	6.6	1.3	0.9	0.71	9.7	7.7	0.8	1.16	1.41
33	7.0	4.0	1.8	1.11	0.6	7.6	3.5	2.4	1.59	0.65
34	5.3	4.1	0.8	0.34	0.43	5.8	4.0	1.4	0.35	0.25
35	10.1	6.9	1.7	1.01	0.58	10.4	6.3	2.7	1.14	0.42
36	6.2	3.3	1.7	0.99	0.59	6.4	3.9	1.7	0.67	0.39
37	12.0	9.3	1.3	1.32	1.04	12.2	8.2	2.2	1.7	0.77
38	8.1	5.7	1.7	0.52	0.3	8.1	5.1	1.9	0.81	0.42
39	5.4	3.5	0.8	0.78	0.93	5.2	3.3	1.2	0.57	0.48
40	15.5	12.0	2.2	0.93	0.41	15.2	12.1	1.7	1.06	0.6
41	8.8	5.9	2.0	0.79	0.39	8.3	5.8	1.7	0.66	0.38
42	8.1	5.4	2.2	0.2	0.09	7.0	4.1	2.4	0.39	0.16
43	13.3	10.3	1.7	1.2	0.69	11.6	9.1	1.5	0.93	0.64
44	7.9	5.3	1.5	0.98	0.65	6.1	4.2	1.2	0.7	0.58
45	8.5	4.6	2.7	0.89	0.33	6.8	5.1	1.0	0.47	0.45
46	8.3	5.8	1.7	0.58	0.35	6.4	4.0	1.6	0.54	0.34
47	8.9	5.7	2.4	0.71	0.29	6.4	4.3	1.5	0.51	0.33
48	10.9	7.3	2.3	0.92	0.39	7.7	4.6	2.3	0.66	0.28
49	11.9	7.7	3.0	1.13	0.37	8.0	4.5	2.3	1.00	0.43
50	11.8	6.8	3.1	1.7	0.54	6.7	4.2	1.8	0.53	0.3

The interpretation of the leukocytic picture in pulmonary tuberculosis is based on the concept that each cell type plays a certain rôle in the tuberculous process. The polymorphonuclear leukocyte is regarded as the chief cell in the formation of tuberculous abscesses, the monocyte is principally concerned in tubercle formation and the lymphocyte is associated with processes of repair. Predominance of a cell type or an increase or decrease of one or more of these cell types in the peripheral circulation are thought to reflect the status of the tuberculous lesion. Obviously, variations in the leukocytic picture due to alterations in the physiologic state of the patient may obscure the true condition of the case. Such physiologic variations may be eliminated to a certain extent by doing the leukocyte count under basal conditions.

Summary. 1. In 50 tuberculous patients leukocyte counts were made after 1 hour's rest in bed and the results compared with those of blood counts taken after some exercise.

2. Thirty-eight cases showed an increase in their total counts following exercise (increases of more than 2000 cells were obtained in 19 cases); 12 cases showed a decrease in their total counts taken after exercise.

3. Striking variations were noted in some of the differential counts taken after exercise; increases in the cells of some types exceeding 100 per cent were encountered.

4. The value of performing leukocyte counts under basal conditions in the study of cases with pulmonary tuberculosis is emphasized.

NOTE. I wish to express my appreciation to Dr. Sumner H. Remick, superintendent of the Middlesex County Sanatorium, for his interest in this study.

I am indebted to Miss Olive F. Allebaugh for much valuable technical assistance.

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SPONTANEOUS CEREBRAL VASCULAR ACCIDENTS IN DIABETES.

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ARTERIOSCLEROSIS is now the chief foe of diabetics, causing 48 per cent of the deaths in the late Banting era (Joslin, 1930). Among the fatal cases due to arteriosclerosis in the entire Banting era.

predilection was shown for the heart in 43 per cent, for the peripheral arteries in 30 per cent, and for the brain in 16 per cent. Root and Graybiel (1931) of this clinic have described the most important phase of arteriosclerosis of the heart, and McKittrick and Root (1928) have described such disease of the peripheral arteries. We now present a brief report of the third most important group of arteriosclerotic, diabetic patients: those suffering from cerebral vascular disease, which causes 7 per cent of all diabetic deaths (Joslin, 1930).

The present report deals with 70 unselected (except as stated below) cases of cerebral vascular accidents in Dr. Joslin's diabetics. Most, but not all, of the cases had some sudden attack which left evidences of a unilateral brain lesion, such as hemiplegia or hemianopsia. A few of the cases had a more gradual onset of their trouble, suggesting thrombosis. The degree of involvement varied from weakness of the right hand associated with speech defect of 2 days' duration to complete unconsciousness and hemiplegia resulting in death. All of the cases can be classified as suffering from apoplexy. Cases due to embolism, inflammatory lesions, brain tumor or trauma were excluded.

The age at onset of the apoplexy varied from 46 to 77 years with an average of 62.2 years for the 70 cases as opposed to an average age of 50 years found by Webster (1929) in a series of 125 cases of cerebral hemorrhage, only 2 of which were known diabetics although 6 others had glycosuria. This agrees with Root and Graybiel's (1931) finding of an average age of 60 years at onset of angina in diabetics as compared with that of 57 years in non-diabetics (White, quoted by Root and Graybiel). In Webster's series there were 92 males and only 33 females. In our series there was a reversal of sex distribution, 52 females and only 18 males. A similar though less marked reversal of the male sex preponderance in angina pectoris was noted by Root and Graybiel in their diabetic angina series. Webster reported that the lesion was on the right in 53 per cent of his cases as opposed to a far greater predominance on the right as noted by earlier observers. In our series in 38 instances the lesion was on the right and in 40 on the left.

The degree of incapacity varied markedly. Of the 70 patients, 31 are dead; 4 cases died within a short time from the shock and 2 others succumbed to coronary thrombosis within a week of the shock; a total of 11 cases died within less than a year. Of the 39 living cases none is completely incapacitated either physically or mentally. One case has carried out his duties as a judge for 14 years since the onset of apoplexy; he is now 75 years of age. The average duration of life after the first shock for both living and dead cases is 3.4 years. These observations are most encouraging, and they contrast sharply with Webster's (1929) statement that 90 per cent of his cases died within a month. Moxon (1926) noted

that 90 per cent of the cases of cerebral hemorrhage died within 24 hours.

Possibly one can compare the condition of the circulation in the brain with that in the extremities. In diabetic gangrene the slow development of intimal changes encourages an extensive collateral circulation in the legs (McKittrick and Root, 1928). Perhaps a similar mechanism in the cerebral circulation helps to reduce the number of rapidly fatal vascular accidents.

Root and Graybiel (1931) stated that "The diabetic patient with angina has a poorer prognosis than the non-diabetic patient." This may be due to the fact that, because of the relative insensitivity of the diabetic with poor circulation, organic disease of the coronary vessels and the myocardium may be further advanced when the symptoms of angina pectoris appear than in the non-diabetic. In following up these groups and in studying new cases treated by more modern dietary methods, a change in the prognosis may be found. During 1933 Dr. Root will reinvestigate the question of circulatory disease in diabetics.

Fifteen cases had more than 1 attack of apoplexy and 5 of these are still alive. In fact one man with diabetes of 19 years' duration is still alive after 3 such attacks. Of the 15 cases 9 died as a result of the second shock, and the 10th died with coronary thrombosis 3 days after the second shock. The average interval between attacks was 1.7 years. The average age at death for the fatal cases was 65.5 years, but it must be remembered that 39 of these 70 cases are still living.

Of the 31 fatal cases 14 died of cerebral disease, 8 of arteriosclerotic heart disease, 3 of pneumonia, 1 of gangrene, 1 of nephritis, 1 of diabetic coma, 1 of peritonitis, 1 of volvulus, and 1 of an unknown cause.

In the etiology of the condition arteriosclerosis and hypertension were the two outstanding factors. Arteriosclerosis in one site or another was recognized in 64 of the 70 cases, an incidence of 91.4 per cent as opposed to Webster's (1929) series of 68.7 per cent. Coronary disease was present in 15 cases, and 2 others had heart disease presumably of arteriosclerotic origin. There were 11 cases of gangrene. Two of the apoplectics had both gangrene and coronary disease, 1 of whom died at the age of 50 years, having had diabetes 15½ years. Of the 70 cases 48 had hypertension. The diagnosis of hypertension was made from the history alone in 3 cases, and no figures were stated. Our criterion for hypertension was either a systolic pressure of 170 mm. or more or a diastolic of at least 100 mm. The average maximum systolic pressure in the remaining 45 cases was 206 mm., the average diastolic 107 mm. of mercury. Hitzenger (1921) found that elderly diabetics had a higher blood pressure than non-diabetics of a similar age group. Major (1929) confirmed this as to the systolic pressure. However, Adams (1929) found no

definite evidence that diabetes *per se* promotes hypertension. Joslin (1928) gives an average systolic pressure of 154 mm. for 100 diabetics over 50 years of age. Excluding the 3 patients on whom a diagnosis of hypertension was made elsewhere and for whom we lack the figures, we find in the remaining 67 cases an average maximum systolic pressure of 188 mm. and an average diastolic of 98 mm. Webster (1929) found in 105 cases of cerebral hemorrhage an average systolic pressure of 177 mm. and a diastolic of 104 mm.

The incidence of apoplexy of 7 per cent among fatal diabetics (Joslin, 1930) and of 8.4 per cent in 2400 autopsies at the Cleveland City Hospital (Webster, 1929) would imply that there is little to incriminate diabetes as an etiologic agent in the production of apoplexy. On the other hand embolism, inflammatory lesions (including syphilis), and neoplasm may have increased the incidence in Webster's series, whereas we have eliminated such cases from our series. In our 70 cases the diabetes began before the apoplexy in 60 cases with an average duration of 6.3 years prior to the apoplexy, with extremes of 0.5 to 27 years. In 6 cases the diabetes apparently developed after the apoplexy, and in the remaining 4 cases at the time of the apoplexy. Of the 70 cases 50 were classified as mild diabetics, 17 as moderate and 3 as severe requiring more than 30 units of insulin a day. In 54 of the cases insulin was administered at one time or another, and 45 cases had received insulin prior to the attack.

Four of the cases developed diabetes at the time of the apoplexy. Each was a case of mild diabetes and only 1 of these was ever given insulin. This suggests that these 4 cases may be similar to those mentioned by Potter and MacGregor (1925), Elliott (1926), Collier (1931) and Rømcke and Skouge (1931). These authors described cases with glycosuria resulting from cerebral hemorrhage, and Elliott found a blood sugar of 995 mg. per 100 cc. which yielded only partially to 260 units of insulin during the next 48 hours. Potter and MacGregor (1925) and Rømcke and Skouge (1931) found acetonuria as well as glycosuria. It is well known that at times injuries to the midbrain may cause glycosuria, and it is well to remember this when one sees a case with a sudden onset of coma, glycosuria, and even acetonuria. We have one case (No. 10834) not included in this series, who had such a sudden attack, and his local doctor gave him 40 units of insulin daily for a few days; 4 weeks later a sugar tolerance test showed no evidence of diabetes. Munch-Petersen (1931) has devised a test with adrenalin to distinguish between glycosuria of cerebral and pancreatic origin. We have not used this test, and cannot comment on its merits.

The treatment of the apoplexy has been merely symptomatic, including rest and diabetic treatment. In 9 cases insulin therapy was initiated at the time of the attack. One might infer that the cerebral hemorrhage *per se* exaggerated the diabetes or even caused

it, but the inactivity might well be the important factor here. Realizing the dangers of hypoglycemia and sudden alterations of the water balance in patients with arteriosclerosis or hypertension, we have avoided lowering the blood sugar too suddenly or to too great an extent. Insulin is begun in small doses and increased gradually as necessary; and blood sugar determinations 3 to 4 hours after the injection of insulin are made to guide us in such therapy. Blotner (1930), Root and Graybiel (1931), and Parsonnet and Hyman (1931) have shown the influence of hypoglycemia on the occurrence of angina pectoris and coronary thrombosis. Lawrence and Hollins (1928) have reported 2 cases of hematuria attributed to insulin therapy. Among Joslin's diabetics are 25 cases of convulsions during hypoglycemia; and Miller and Trescher (1927), Ravid (1928), Joslin (1928), and Criscitiello and Messer (1931) have all reported insulin paralyses of a hemiplegic nature. It thus becomes obvious that hypoglycemia should be avoided in such a condition as apoplexy, or better still in any person who is a potential apoplectic. Nevertheless it is equally wise to prevent too high a blood sugar or the development of acidosis, and these two requirements are not incompatible if frequent blood sugar determinations and urinalyses are made.

Specific treatment for the apoplexy, such as repeated spinal drainage, has not been attempted by us, although Collier (1931) reports good results from it. Indeed Weiss (1929), Cobb (1931), and Collier (1931) refer to the damage caused by edema and pressure; and decompression therefore might give real relief, especially as Cobb (1931) has shown that there is sufficient collateral blood supply in the brain, provided edema does not occlude it. On the other hand, Kahler (1920) found that in 30 people with brain disease the blood pressure rose in 29 cases after lumbar puncture. Meyer (1923) found that 10 cc. of 20 per cent glucose intravenously lowered the blood pressure in essential hypertension. Allen (1920) maintained that hypertension in diabetics will respond to general and diabetic treatment. A comparison of our series with that of Webster's non-diabetics (1929) reconciles us to simple and time-honored symptomatic treatment.

Summary and Conclusions. Clinical data on 70 cases of cerebral vascular accidents in diabetics are presented, giving the incidence, age of onset, prognosis, etiology and treatment. Arteriosclerosis and hypertension seem to be the most important etiologic agents in the causation of such accidents.

The data suggest that apoplexy in diabetics is not such a hopeless condition as might have been feared; there is some evidence that diabetics withstand cerebral accidents even better than non-diabetics. However, the findings show that diabetics subject to arteriosclerosis in one site are prone to have manifestations of arteriosclerosis elsewhere.

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ROENTGENOGRAPHIC DEMONSTRATION OF AN ARTERIO- VENOUS ANEURYSM BY MEANS OF THOROTRAST.

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ARTERIOGRAPHY is being rapidly perfected. Progress has been due mainly to the use of thorium dioxid prepared in stabilized, colloidal, radio-opaque solution under the trade name of Thorotrast Heyden. This substance has been employed by Radt¹ and others since 1929 for roentgenographic "visualization" of the liver and spleen. One of us (Yater²) has used this method of hepatosplenography in 100 patients during the past 2 years without noteworthy harmful effects.

Arteriography with Thorotrast has been used successfully by a number of investigators.^{3,4,5,6,7,8,9} For this purpose the Thorotrast is injected directly into the artery, a tourniquet being tightly applied above the site of injection. For the arm 10 cc. is ample, but for the leg 20 to 25 cc. is necessary, both these amounts being much smaller than those used for hepatosplenography. After the Thorotrast has been injected into the arterial lumen the tourniquet is loosened for a brief moment to allow the radio-opaque substance to circulate through the limb and then tightened again. Roentgenograms are taken with the tourniquet applied, several different positions of the extremity being used for exposures. When the tourniquet is released the Thorotrast quickly becomes diluted and the blood in the arteries of the extremity is no longer radio-opaque. Some experience is necessary in the proper interpretation of the films, since density and extent of filling of the vessels vary with the technique.

Successful "visualization" of an arteriovenous aneurysm has been reported only once in the literature. This was in a case reported by Horton¹⁰ in the *Proceedings of the Staff Meetings of the Mayo Clinic* some weeks after our patient had been studied. In Horton's report the Roentgen opaque medium used was not stated. The case was one of an abnormal communication between the femoral artery and vein produced by birdshot. The fistula was not especially well demonstrated in the film. In congenital arteriovenous fistulas the communications between the small arteries and veins are usually so numerous that good definition is practically impossible. There seems to be no reason, however, why a traumatic fistula in many cases cannot be well brought out and its architecture and site carefully studied before operation. The following case illustrates successful "visualization" of an acquired arteriovenous fistula, connected with which there was a small aneurysmal sac.

Report of Case. The patient, a negro boy, aged 15, entered this hospital on February 26, 1933, without a chief complaint of his own. He had been referred because of enlargement of the heart of unknown cause. This had been discovered in the syphilis clinic, where he was being treated because of a positive blood Wassermann reaction. His health had always been good except for measles, mumps and chickenpox. Five months previously he had received a load of buckshot from a shotgun in the right arm. His arm had been swollen and blue immediately afterward, but these signs had gradually disappeared with complete disability of the extremity. Physical examination was normal except for the heart and the right arm. The heart was moderately enlarged, the apex beat being 8.5 cm. from the midsternal line in the 5th left intercostal space. There was a soft systolic murmur at the apex and a higher pitched systolic murmur at the base. The second aortic sound was accentuated. The right arm and forearm were visibly larger than the left. The length of both



FIG. 1.—Roentgenogram of the right forearm with the palm upward. The numerous opaque spots are buckshot. *b*, brachial artery; *r*, radial artery; *u*, origin of ulnar artery; *s*, sac of the arteriovenous aneurysm; *r.*, vein draining the aneurysm.

arms was 48 cm. The circumferences of the arms at various points were as follows: Arm, 7 cm. above olecranon process: 22 cm. left, 23.8 cm. right. Forearm, 7 cm. below olecranon process: 23.5 cm. left, 24.75 cm. right. Forearm just above wrist: 15.2 cm. left, 16 cm. right. Hand below thumb: 20 cm. left, 20.4 cm. right.

A number of small scars in the antecubital fossa and its neighborhood were present where the buckshot had entered. The movements of the extremity were normal. Trophic lesions and color changes were not noted, and the superficial veins were not dilated. A loud humming sound with systolic accentuation was heard with the stethoscope in the right side of the neck and down the entire length of the right arm. It was audible even at the tips of the fingers. The greatest intensity of the murmur was in the antecubital fossa nearer the ulnar side. A thrill was palpable in the extremity, but its distribution was not as great as that of the bruit. Its point of maximum intensity was much more definite than that of the murmur, being about 5 cm. below the middle of the antecubital fossa on the ulnar side. The heart rate was 80 per minute, and the rhythm was regular. The systolic blood pressure was 140 mm. Hg and the diastolic 80 mm. Hg in the left arm; in the right arm the systolic pressure was also 140 mm. Hg, but the diastolic pressure could not be determined, the sounds being heard loudly down to the zero point. Closure of the fistula by compression over the point of maximum thrill did not alter the pulse rate appreciably, but the systolic blood pressure in the left arm dropped to 130 mm. Hg. The Kahn test of the blood was 4+; hemoglobin, 88 per cent (Newcomer); leukocytes, 5200 per c.mm. The urinalysis was normal. Determination of the oxygen content of the blood in the superficial veins of the right arm showed that the blood was practically arterial. A roentgenogram of the chest revealed moderate enlargement of the heart.

A long sharp needle attached to a syringe containing 10 cc. of Thorotrast was inserted through the skin over the right brachial artery at about its middle. An anesthetic was not employed. The artery was pierced, and a tourniquet was immediately drawn tightly about the upper part of the right arm. The Thorotrast was injected into the artery and the needle then withdrawn. The tourniquet was loosened slightly for a brief instant in order to allow the blood to flow, and then drawn tight again. A roentgenogram (Fig. 1) was then taken with the tourniquet in place. This shows that the ulnar artery passes into a sac, undoubtedly venous, from which the blood flows back up through the arm in a large vein. The film shows the exact location and shape of the aneurysm. Permission to operate could not be obtained.

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AN AURICULOSYSTOLIC MURMUR IN THE "TRICUSPID AREA" DURING CONVALESCENCE FROM ACUTE CORONARY OCCLUSION.

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DURING the past year, we have twice had the opportunity of hearing high-pitched auriculosystolic murmurs in the "tricuspid area," which have apparently developed and then disappeared during convalescence from acute coronary occlusion. We are unaware of any previous reference to this phenomenon in the literature.

Case Abstracts. CASE 1.—D. F., a Russian Jew, aged 67, was known to have had diabetes mellitus since 1925. In 1931 his right leg had been amputated for threatened gangrene. On March 11, 1932, he was admitted to the medical service in this hospital, because of circulatory deficiency in the left leg. On March 15, he developed upper abdominal pain of moderate severity and vomited several times. The next day the temperature rose to 101° F.; the pulse rate became accelerated; the blood pressure dropped from 200 systolic and 85 diastolic to 100 systolic and 50 diastolic; râles appeared at the lung bases; and a leukocytosis (14,000) developed. The fever and leukocytosis continued for 10 days. The patient suffered transient attacks of auricular fibrillation for several days. Electrocardiograms showed definite deviations of the *RS-T* interval from the isoelectric line which disappeared after 12 days. All the findings were typical of acute cardiac infarction. The character of the electrocardiogram (Fig. 1-A) suggested that the lesion was located in the anterior surface of the left ventricle, in the distribution of the left anterior descending coronary artery.¹

On March 30, a soft, high-pitched, blowing presystolic murmur was heard in the 4th interspace just to the right of the sternum. Its area of audibility included the sternum and the region 2 or 3 cm. to either side of it between the 3d and 5th interspaces. The intensity of the sound increased for several days and then diminished. It disappeared 8 days later. (Fig. 1-B shows a simultaneous phonocardiogram and electrocardiogram recorded without parallax). The patient subsequently made a fair recovery and was discharged on May 11.

CASE 2.—M. G., a Polish Jew, aged 54, was apparently in his normal state of health until November 5, 1932, when he had an attack of pain. 20 minutes in duration, centering beneath the lower sternum, extending over the precordium, and radiating down the left arm. The next morning

after breakfast he suffered a similar attack. On November 10, he visited the Out-Patient Department of this hospital and while waiting on a bench was again seized with severe pain about the heart. As the attack did not pass off, he was referred to the ward on the service of Dr. Alfred Stengel. The pain lasted 24 hours, requiring morphin to make it endurable. The blood pressure, which on admission was 140 systolic and 90 diastolic, dropped slightly to 120 systolic and 70 diastolic that afternoon. Râles appeared at the lung bases. Fever and leukocytosis developed the next day, and persisted for a week. Disturbances in cardiac rhythm were frequently noted. There were many extrasystoles. Transient paroxysms of tachycardia, auricular fibrillation and heart block were observed and graphically recorded. Electrocardiograms were obtained 3 hours after the onset and repeatedly after that. They showed deviations of the *RS-T* interval from the isoelectric line which disappeared after 14 days. Most of the classical features of recent cardiac infarction were present. The electrocardiograms (Fig. 2-A) suggested that the lesion was located in the anterior surface of the left ventricle.¹

The patient's heart was ausculted carefully each day. On November 15, 5 days after admission, a soft high-pitched blowing presystolic bruit was heard over the sternum, and to either side of it, at the level of the 3d, 4th and 5th interspaces. The sound seemed to increase in intensity for about 9 days and it then began to diminish. On December 4 it was quite indistinct. and 2 days later, 22 days after it first became audible, it disappeared. (Fig. 2-B is a simultaneous phonocardiogram and electrocardiogram recorded without parallax.)

During one attack of partial heart block, it was obvious that this murmur was related to auricular rather than to ventricular activity. During several attacks of auricular fibrillation, the murmur seemed to disappear. However, on November 29, during an attack of auricular fibrillation, the murmur was heard by several observers. At this time it occurred in early diastole shortly after the second sound and was inaudible in the presystolic period.

The patient recovered slowly. He was discharged on December 31. He was last seen on January 23, 1933, at which time he was much restricted by his cardiac lesion.

Discussion. We have no data concerning the frequency of this parasternal, auriculosystolic murmur in coronary occlusion. Because of its location and character it might readily pass unnoticed. It may not be very uncommon, since we were able to discover a second case within a year. The quality of this murmur, and its point of audibility over the "tricuspid area," are unusual enough to make its presence of possible diagnostic assistance in certain cases.

In one case the murmur was heard from the 15th to the 23d day. In the other, it was first heard on the 5th day and disappeared on the 27th. It seems logical, therefore, to believe that it was, in both cases, etiologically related to acute coronary occlusion.

The mechanism of production of this sound is not clear. Murmurs of this type have been described with patent foramen ovale. However, such an etiology seems unlikely in these cases, because of the time relations of the appearance and disappearance of the murmur to the acute coronary occlusion. The possibility of an auricular friction was considered. It was discarded because of the length of

time during which the sound persisted, and because the bruit did not disappear during auricular fibrillation.

The evidence at hand concerning the cause of this murmur might be stated as follows: (1) The place at which it was best heard suggests that it is dependent upon some disturbance in the neighborhood of the tricuspid valve. (2) It resembled the presystolic murmur of mitral stenosis with respect to its relation to auricular activity. During normal rhythm and during partial heart block, it followed the *P* wave of the electrocardiogram. During auricular fibrillation it became more difficult to hear; it began in early diastole, shortly after the second sound, and was inaudible in the presystolic period. (3) Both of the cases in which this murmur appeared were probably instances of occlusion of the left anterior descending coronary artery with infarction of the anterior surface of the left ventricle. Neither of them came to necropsy, but the electrocardiographic evidence of location was quite definite.¹ (4) We examined a number of pathologic specimens of hearts with anterior infarction, to determine if any structural change could be found which might account for this murmur. A mural thrombus lying beneath one of the tricuspid leaflets might be able to produce such a bruit, but none of the specimens of anterior infarction had a thrombus in this location. Many showed a thinning of the anterior part of the interventricular septum and a bulging of this structure into the right ventricle. Edema of the tissues in and near the infarct was quite constant. One specimen with a posterior infarction, from occlusion of the right coronary artery, showed a thrombus lying beneath the posterior leaflet of the tricuspid valve.

We must conclude, thereafter, that this murmur is probably related to convalescence from acute coronary occlusion; and that it seems to be produced by the flow of blood from right auricle to right ventricle. We do not know just why this flow of blood causes a sound; possibly because the structures near the tricuspid valve are edematous; possibly because the interventricular septum is thin and bulges into the right ventricle; possibly, in certain cases, because mural thrombi occur in the right ventricle in such a position as to interfere with the opening of the tricuspid valve.

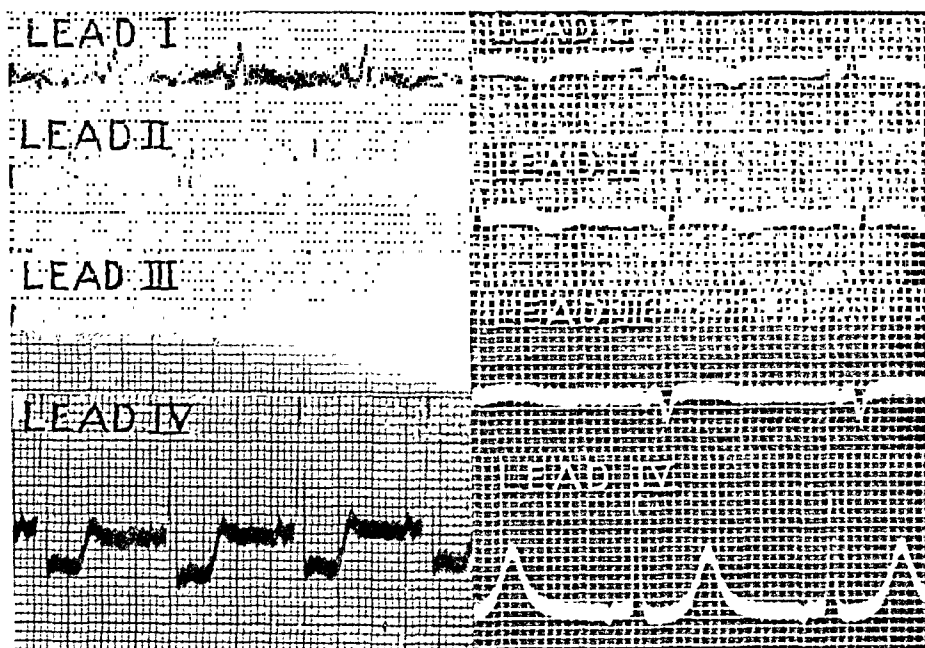
Summary. In two cases of cardiac infarction, an auriculosystolic murmur was heard over the "tricuspid area" during convalescence.

In one case it was first discovered on the 15th day and disappeared on the 23d. In the other, it developed on the 5th day, and disappeared on the 27th.

In both instances the infarct was probably located in the anterior surface of the left ventricle.

In one case, the behavior of the sound was observed during partial heart block, and during a paroxysm of auricular fibrillation.

The data at hand suggest that the sound is produced in some way by the flow of blood from right auricle to right ventricle.



B

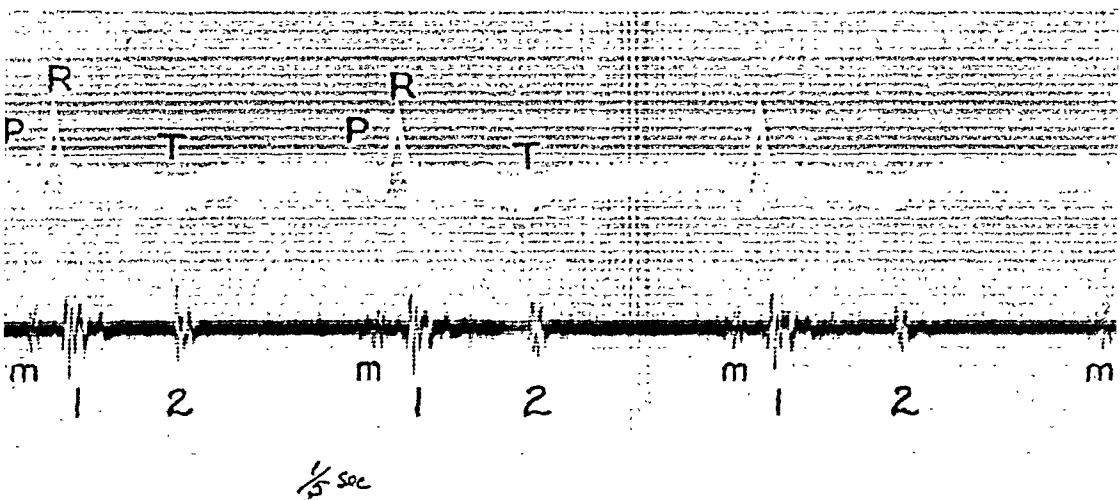
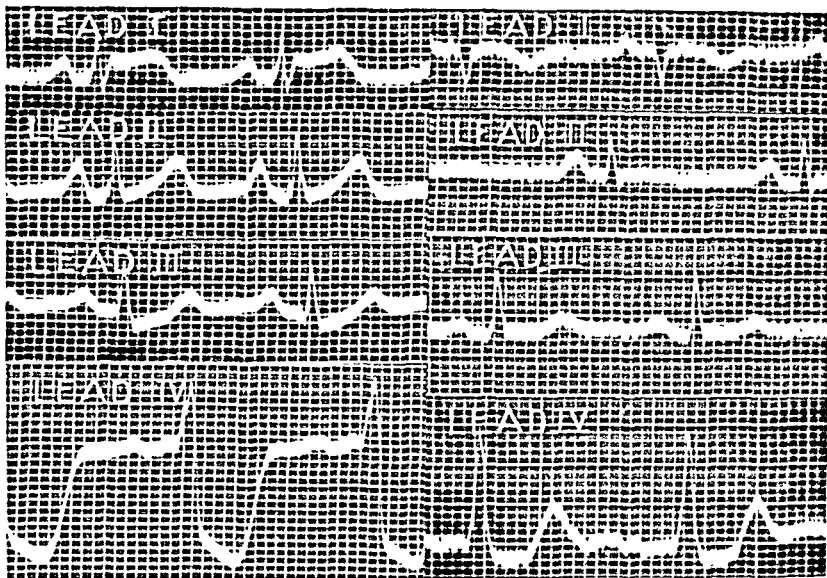
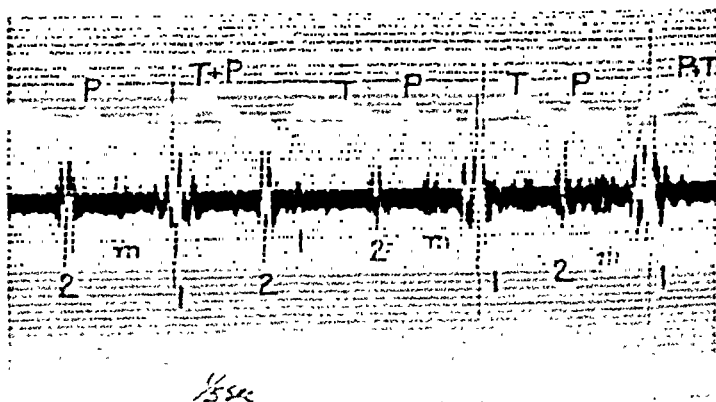
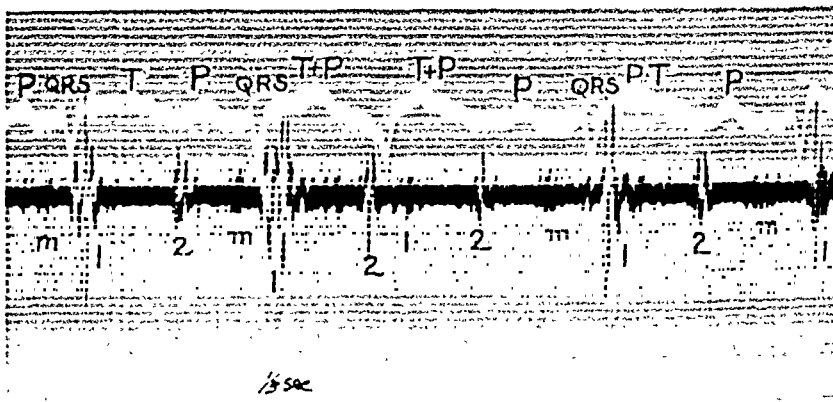


FIG. 1.—Tracings of Case 1. A. Electrocardiograms taken on March 24 and March 30, 1932. Four leads were used.² The tracing on March 24 shows a cove plane *T* wave in Lead I, and a slight elevation of the *RS-T* interval in Lead II. Lead IV (the anteroposterior chest lead) shows an absence of the initial downward deflection of *Q-R-S*, and a marked depression of the *RS-T* interval. The tracing taken on March 30 shows an inverted *T* wave in Leads I and II. Lead IV shows that the initial downward deflection of *Q-R-S* is still absent; a high upright *T* wave has made its appearance. The *RS-T* interval depression has disappeared. This type of tracing is probably indicative of an infarct in the anterior surface of the left ventricle, in the distribution of the left anterior descending coronary artery.¹ B. Simultaneous electrocardiogram and phonocardiogram recorded without parallax (March 30, 1932). "1" marks the first heart sound; "2" marks the second heart sound; "m" marks the vibrations produced by the "auriculosystolic murmur." Time intervals in $\frac{1}{3}$ seconds are shown at the bottom of the tracing.



B



The characteristics of the murmur, and its area of audibility are unusual enough to make its occurrence of possible diagnostic assistance in some cases.

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LEGEND FOR FIG. 2.

FIG. 2.—Tracings of Case 2. A. Electrocardiograms taken on November 10, 1932, and on January 23, 1933. Four leads were used.² The tracing taken on November 10, 1932, shows an elevation of the *RS-T* interval in Lead I, and a slight depression of this interval in Lead III. Lead IV (the anteroposterior chest lead) shows an absence of the initial downward deflection of *Q-R-S*, and a marked depression of the *RS-T* interval. The tracing taken on January 23, 1933, shows an inverted *T* wave in Lead I and an absence of the *T* wave in Lead II. Lead IV still shows the absence of the initial downward deflection of *Q-R-S*. The *RS-T* interval depression is very small. The *T* wave is upright and large. These tracings indicate the probability that this patient's lesion was in the anterior surface of the left ventricle, in the distribution of the left anterior descending coronary artery.¹ B. Simultaneous electrocardiogram and phonocardiogram recorded without parallax. This is a continuous tracing, which had to be cut in two for reproduction. "1" signifies the first heart sound; "2" signifies the second heart sound; "m" marks the auriculosystolic murmur. Time intervals are indicated below in $\frac{1}{2}$ seconds. Partial heart block is shown in the electrocardiogram.

ATYPICAL TYPHOID FEVER. HEART BLOCK. MYOCARDITIS POST-TYPHOSA (ROMBERG). VALUE OF ATROPIN TEST.

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(From the Department of Semiology.—Prof. Dr. T. Padilla.)

It is a well-known fact that our present conception of rheumatic fever is very different from the one we had not long ago; especially the extra-articular localizations (heart, lungs, skin, ocular and nervous system) are very important and not uncommon. We are justified in thinking of rheumatic fever "in all obscure acute illnesses" (Loeb¹). However, we must not carry this idea too far, as is sometimes inevitable, so long as the true etiology of rheumatic fever remains as obscure as it is at present.

It is usually considered that an acute infection with an increased conduction time (electrocardiogram with *P-R* interval of more than 0.20 seconds) is probably rheumatic fever, if diphtheria, pneumonia and influenza have been excluded. This is generally true, but I add that typhoid fever must also be excluded. I wish to emphasize

that an atypical case of typhoid fever can pass unrecognized and be regarded erroneously as rheumatic fever with primary localization in the heart, on account of fever, slight joint pains and auriculo-ventricular block.

If we analyze the opinions expressed on the etiology of heart block, it is found that acute infections have a large importance, especially, rheumatic fever (Cohn and Swift²), diphtheria, pneumonia and influenza (Wilson²). In the latest German books on Internal Medicine (Brugsch,³ v. Bergmann and others⁴), no reference is made to the *P-R* interval in typhoid fever. In American textbooks on medicine (such as those edited by Cecil,⁵ Osler-McCrae,⁶ Blumer⁷) heart block of the degree we are considering is not sufficiently analyzed. In Osler-McCrae⁸ it is merely stated that a delayed auriculoventricular conduction may be observed. In the most recent of American books on internal medicine (Musser⁹), it says: "Electrocardiographic tracings often reveal a prolongation of the *P-R* interval." White¹⁰ says: "certain infectious diseases such as rheumatic fever and diphtheria from which recovery may take place without persistence of heart block . . ." and also "in occasional cases (typhoid fever) delayed auriculo-ventricular conduction can be found by electrocardiogram."

I believe that this indicates that typhoid fever is not considered an important cause of delayed auriculoventricular conduction among the acute infections. I am convinced that not only typhoid fever, but also many acute infections can produce this type of heart block, and that to have good information on the matter it is only necessary to make electrocardiograms of all cases of acute infectious diseases.

I wish to emphasize the fact, that instead of typhoid fever the erroneous diagnosis of acute rheumatic fever may be made, if too much stress is given to the association of fever and heart block, supposing that diphtheria, influenza and pneumonia have been excluded. I shall also refer to the value, at the first sign of typhoid fever, of the Marris atropin test in my experience, when it is not possible (first week of disease) to practice the Widal test. With Charowsky¹¹ and Treston¹² I regard the atropin test as a very important one for the diagnosis of typhoid fever, and recommend it when other tests are unavailable.

I also wish to refer to a case of slight heart failure of late appearance in the convalescence of typhoid fever, which has been so well described by Romberg¹³; the myocarditis post-typhosa, that is due to typhoid fever, but appearing after the infection has gone. The myocarditis that appears during the disease may be called typhoid myocarditis.

The myocarditis post-typhosa is very rare, and not sufficiently considered in the books on internal medicine. My observations are of interest, because it has been possible to study the state of

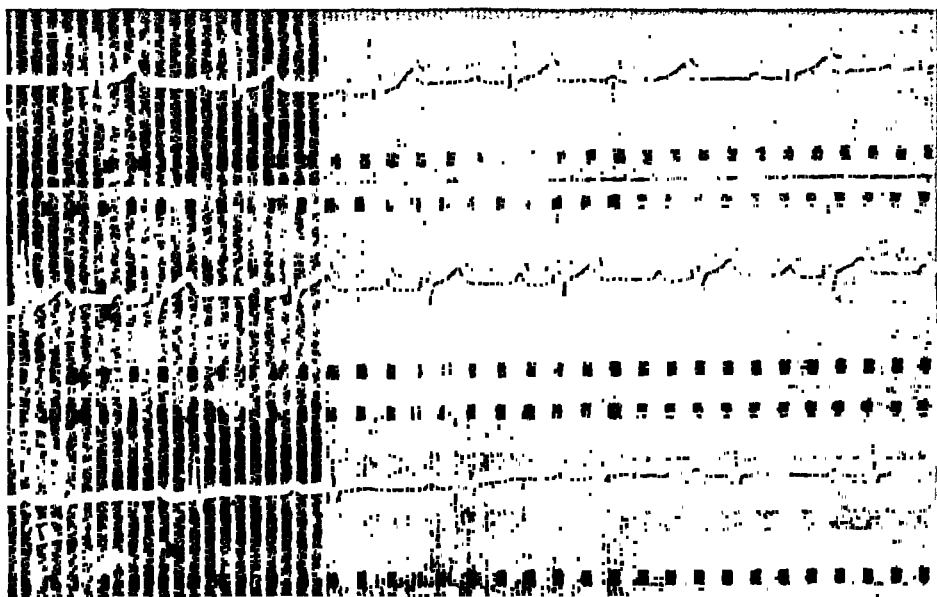


FIG. 1.—Electrocardiogram of Case 1, showing delayed conduction time, October 21, 1932. *P-R*, 0.24 seconds.

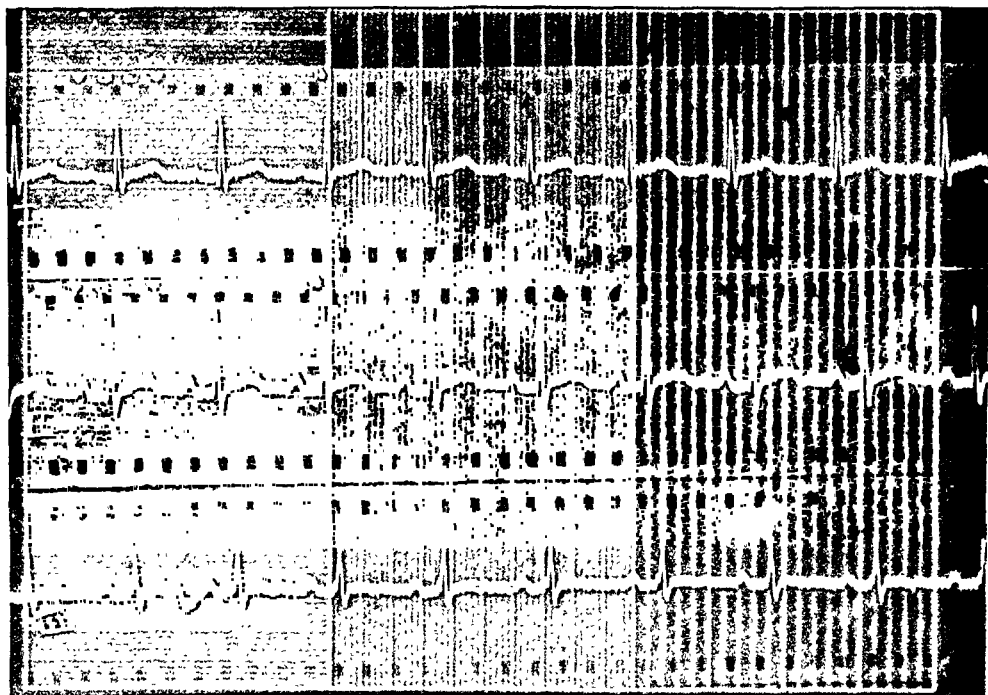


FIG. 3.—Electrocardiogram of Case 1, on October 30, 1932, *P-R*, 0.20 seconds.

blood gases and circulation rate during the state of slight heart failure, and when the patient was cured altogether.

Typhoid fever is a disease that with the advance of preventive medicine must be greatly reduced. The United States have made a great progress in this respect. Barker¹⁴ says: "Nowadays it is often very difficult in our medical clinics in the East to find a single case of typhoid fever for teaching purposes" and adds that F. Müller, the distinguished head of the Medical Clinic (Munich), told him "that it was most rare for him to find a case for discussion before his students." In Buenos Aires we also have a decrease in the incidence of typhoid fever, so it is justified to relate cases that are of especial interest, either on account of difficulties of diagnosis, or complications of unusual character.

Abstract of Cases. CASE 1.—L. G. B., Argentine, white, aged 22, 73 kg. 200, 1.78 m., single, workman, became acutely ill, with chills, fever (39°) pains in joints and extremities, slight abdominal pains. The next day he took a purgative; there followed several bowel movements, but he felt no better. On the 3d day a physician was called; fever was high (41°). An ice bag on the abdomen was ordered and cachets with quinin. The patient improved somewhat, but on account of persistence of high fever went to the "Hospital de Clinicas" and was admitted on the 4th day of his illness.

Past History. He had measles at 9, and acute tonsillitis with a phlegmon. at 17. The acute state passed, tonsillectomy was performed. No venereal diseases.

Physical Examination. Thirty-nine degrees, he has a good appearance, no typhus. Head and neck without abnormalities; lungs normal; liver and spleen not enlarged. Abdomen: meteorismus, no pain. Extremities: normal. Heart: Normal. Pulse, 80. Blood pressure, 110/65 (Baumanometer-Korotkow), marked dirotism. Electrocardiogram: P-R 0.24 seconds (Fig. 1), Marris atropin test: 9 o'clock, 76. Two mg. of atropin injected.

<i>Time.</i>	<i>Pulse Rate.</i>	<i>Time.</i>	<i>Pulse Rate.</i>
9:25	72	9:39	84
9:32	74	9:40	86
9:35	74	9:41	84
9:36	80	9:42	84
9:37	82	9:43	84
9:38	84	9:45	82

Laboratory Studies. Wassermann and Kahn reactions, negative; blood urea, 0.039 gm. per cent; sugar, 0.09 gm. per cent (21-x-32); red corpuscles, 4,090,000; leukocytes: 7200 (26-x-32) 6500; neutrophils, 75 per cent; monocytes, 5 per cent; eosinophils, 1 per cent; lymphocytes, 19 per cent; blood culture (20-x-32), sterile. Sedimentation rate (Westergren): 1st hour, 32 mm.; 2d hour, 42 mm. Urine: urobilin +, no sugar, no albumin. Stools, no protozoa, no eggs of helminths.

On account of high fever, slow pulse in relation with temperature, marked dirotism, absence of signs of meningitis, a tentative diagnosis of typhoid fever was made. The atropin test was positive.

As this young man had an acute infection, and also at first slight pains in the joints, the auriculoventricular block suggested acute rheumatic fever; but on account of the absence of leukocytosis, of sweats and of

angina, with positive atropin test, and no signs of endocarditis, I maintained the diagnosis of typhoid fever or paratyphoid, and awaited the arrival of the 2d week to perform the Widal test.

I prescribed a high-caloric diet only. No salicylates were given. Fever began to fall by lysis on the 6th day of illness (Fig. 2). On the 9th day he was apyretic and perfectly well. On the 14th day the Widal test was positive at the titer of 1/100 and at more than 1/200 positive for typhoid and negative for paratyphoid. When the patient was discharged the *P-R* interval was 0.20 seconds (Fig. 3).

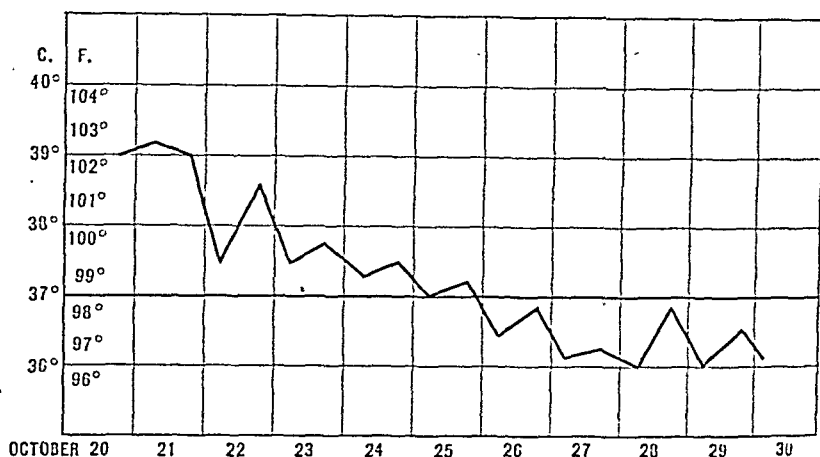


FIG. 2.—Temperature chart.

As this young man was not vaccinated against typhoid, and never had had typhoid fever, it seems to me sufficient proof that his sickness was typhoid fever of an unusually mild course and atypical signs. The importance of a normal leukocyte count is to be emphasized, also the high fever and slow pulse rate, with positive atropin test, and also that although the malady was so mild, it produced a heart damage that in absence of electrocardiogram could not have been detected. While it was impossible to get another record after he was discharged, I believe the block will disappear.

This type of heart-block is probably due to the toxemia and comparable to that observed by Lewis¹⁵ in a young man with a *P-R* of 0.32 seconds who had a cystitis due to coli bacillus. The heart-block disappeared when the cystitis was treated and cured.

CASE 2.—O. A. L., Argentine, aged 14, white; when admitted was in the 9th day of his illness. This began with chills, sweats, 38.5°. On the next day 39.5°, severe abdominal pains and diarrhea began and continued with high fever and delirium until he entered the hospital.

His past history was of no importance.

On examination he had the common aspect of a typhoid patient. The spleen was moderately enlarged. Meteorismus. Blood pressure, 110/70 (Baumanometer Korotkow). Pulse rate, 80. Marris atropin test: positive; 11 o'clock, 88; 11.32, 95. Urine, urobilin, +++; blood urea, 0.01 gm. per cent; sugar, 0.10 gm. per cent; red corpuscles, 3,630,000; leukocytes, 6800; hemoglobin (Sahli), 60 per cent; neutrophils, 85 per cent; eosinophils.

Widal test, positive, 1/50, 1/100, 1/150 (*B. typhosus*).

Comment. This was a common case of typhoid fever. I treated it with the usual high-caloric diet and amidopyrin in the form recommended by Krehl in 1931.¹⁶ To this patient we gave 0.05 gm. of amidopyrin when fever was at 38°. The principles of treatment are to maintain the patient with a temperature between 36.5° and 38°. To obtain this it is necessary to determine the body temperature (axilla) every hour, and give amidopyrin in doses from 0.05 gm. to 0.10 gm., when fever is over 38°. My patient was very delirious, but when amidopyrin was given, the delirium ceased. It has been observed that many symptoms attributed to toxemia are due principally to high fever. Following the treatment recommended by Krehl, the temperature must also be determined by night; although sleeping, the patient can be awakened, if necessary, and once amidopyrin is given, he continues to sleep. In my opinion, the doses recommended by Schultz,¹⁷ 0.15 to 0.30 gm., for the treatment of typhoid fever are too large, and that to obtain the best results, the technique recommended by Krehl must be followed. I do not believe that this method has any action that prevents complications or shortens the duration of sickness, but it helps the patient to feel better and makes it unnecessary to move him for bathing.

Myocarditis Post-typhosa. Romberg¹³ says: "The very rare myocarditis post-typhosa (Hayem, Romberg, Thayer) usually appears 1 or 2 weeks after the febrile period has passed, only in some cases immediately after it, with persistence of cardiac manifestations that eventually could have existed before."

CASE 2 (*Continued*).—The symptoms found in this patient began to be observed by him 2 weeks after he was apyretic and at home. He returned to the hospital, saying that he had palpitations, dyspnea and edema of the ankles. When the patient was discharged, he had a pulse rate of 80, and normal blood pressure. When he returned, he had palpitations and the pulse rate was 120 a minute, but regular. Blood pressure 110/80. The auscultation of heart revealed a soft systolic murmur in the mitral area, and heart sounds were slightly reinforced. A teleoroentgenogram revealed a slight enlargement of the heart. The electrocardiogram a sinusal tachycardia. The possibility of post-typhoid hyperthyroidism was considered, but as the patient had gained several kg. in weight, post-typhoid myocarditis was accepted, and also slight heart failure. My colleague and cardiologist of the clinic, Dr. Cossio, did with Dr. Berconski the analysis of the blood gases and determination of circulatory rate, for which I express to them my thanks.

The results were (March 28): Circulation rate, by histamin method: redness of the face, 25 seconds; taste, 28 seconds. Arterial blood: oxygen saturation, 90.3 per cent; venous blood, 54.2 per cent.

(April 14, 1932). Circulation rate: redness, 14 seconds; taste, 17 seconds. Arterial oxygen saturation, 94.7 per cent; venous, 65 per cent.

The patient was treated with insulin, rest and strychnin. He was discharged with an apparently normal heart.

Summary. Two uncommon cases of typhoid fever are related. The importance of the atropin test of Marris is emphasized. One case showed auriculoventricular block (*P-R*, 0.24 seconds) with high fever and joint pains that suggested rheumatic fever; but the

positive atropin test, the absence of leukocytosis, and Widal test, all proved that the diagnosis, typhoid fever, was correct. The disease was of a very short duration, only lasting a week.

The second case showed the good effects of treatment with amidopyrin as suggested by Krehl, and the appearance of the very rare myocarditis post-typhosa (Romberg) and also because it was possible to determine the oxygen saturation (blood gases) during heart failure and after recovery.

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THE ANATOMY OF CHRONIC BRONCHITIS AND BRONCHIAL ASTHMA AS DISCLOSED BY LIPIODOL EXAMINATION.

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THE medical literature for a number of years reveals but little advance in the etiology, pathology or treatment of chronic bronchitis. In fact, it would be substantially true to say that since

Laennec wrote the first clinical and pathologic account of chronic bronchitis, little has been added to pathologic knowledge* and nothing to diagnosis of the condition. Bacteriology has fundamentally modified medical science but, so far as chronic bronchitis is concerned, has only dimmed clinical vision and relegated anatomy and physiology to the background. Bacteriologic invasion is not, in my opinion, the fundamental cause of chronic bronchitis. Roentgen rays, introduced in 1895, and the bronchoscope (1898) have not guided us a step nearer to the diagnosis of the local condition of the bronchial tubes, which, after all, is the most important consideration in treatment.

The only physical signs of chronic bronchitis are fleeting and inconstant wheezing râles and a resonant percussion note over the chest. It is possible to diagnose "chronic bronchitis" by the unaided ear and eye and the patient's story; it has no specific symptoms or physical signs. The condition is regarded by some as an inflammation produced by bacilli, but there is often no clinical evidence of inflammation, and of the many species of microorganisms that may be present, none is constant or specific. Chronic bronchitis is a disease or disordered state of the bronchial tubes. Their anatomic condition is the all-important consideration, but auscultation and percussion do not disclose it, nor does the ordinary radiograph reveal more than shadows which are difficult to interpret accurately. In fact, the anatomy and physiology of "chronic bronchitis" are unexplored fields. The great work of Gaskell and Langley on the sympathetic nervous system has never been applied clinically to bronchitis. The bronchial tree is not an organ consisting of mechanical pipes; it is a system of living channels whose musculature, contracting and expanding under the control of the autonomic nervous system, is constantly altering its caliber. Chronic bronchitis is due to physiologic and pathologic changes in these tubes, and a knowledge of their exact anatomic condition in every case is essential for diagnosis and treatment. This paper is an extension of my Hunterian oration, 1932, on the same thesis.²

The Use of Lipiodol. The injection of lipiodol provides a wonderfully accurate method of ascertaining the anatomic condition of the bronchial tubes. It causes the patient little discomfort and the physician very little difficulty. Moreover, lipiodol has definite and valuable therapeutic effects. It does not irritate and, although it has little if any bactericidal action, it cleanses the respiratory tract mechanically as tea-leaves cleanse a carpet. A certain amount of it is swallowed, but is practically inert in the alimentary canal until it reaches the small intestine, where the pancreatic lipase liberates the iodine. In my opinion all patients labelled "chronic bronchitis" should have the benefit of a diagnostic lipiodol exam-

* Wilson Fox's *Treatise on Diseases of the Thorax*, published posthumously in 1890, is perhaps the most complete study so far as bronchitis is concerned.

ination of both lungs at the beginning of treatment; this examination might with advantage be repeated later to estimate progress and for its therapeutic effect.

After 3 years' experience and a study of over 200 lipiodol cases in chest hospital practice, I can make at least one positive statement: a very small percentage of chronic bronchitis cases show no alteration in the caliber of the bronchial tubes. It is usual to find that some degree of dilatation appears, such as a varicose, beaded or fusiform bronchial tube. The exception is spasmodic asthma, which is closely allied etiologically to chronic bronchitis but is essentially a physiologic dyscrasia with no structural changes and is due to vagal constriction of the smaller bronchioles, which obstructs the passage of air, especially during expiration. Chronic bronchitis, in my opinion, is fundamentally due to dominant sympathetic influences, which cause, among other symptoms, relaxation of the musculature of the bronchial tree. While spasmodic asthma is an exaggeration of the expiratory phase of the respiratory complex, chronic bronchitis may be looked upon as an exaggeration of the inspiratory phase. Expiratory asthma is more evident in the smaller bronchioles, which are relatively more richly supplied with muscular tissue and have relatively more muscular support in their walls and therefore are not so liable to dilatation. The effects of bronchitis are seen chiefly in the medium-sized tubes, where most of the pressure of the explosive cough is felt, and where the walls are relatively less well supplied with muscle, so that when they are frequently in a condition of relaxation, they are liable to become permanently dilated (as in pertussis).

Four chronic diseases of the chest require reconsideration and recasting. Three were first described by Laennec: chronic bronchitis, emphysema and bronchiectasis. The fourth is asthma, which Laennec was the first to attribute to nervous causes, though he was not the first to describe it. All four may now be studied anatomically and physiologically by means of lipiodol. Each has a distinct picture of its own. Each may occur with any or all of the others.

I am including in this summary all cases of "chronic bronchitis" so diagnosed in hospital practice, *i. e.*, cases of chronic bronchitis, emphysema, asthmatic bronchitis and bronchial asthma. I have published elsewhere³ a paper on spasmodic asthma though, strictly speaking, it should be included here.

The crico-thyroid method of giving lipiodol is the one I have used. It is simpler, quicker and gives perhaps better results than the trans-oral, endotracheal, or what may be termed the "sitting up" methods. These require patience, considerable practice, and coöperation from the patient, which is sometimes difficult to obtain. After introducing the lipiodol with the patient lying on the side being injected, and with the table sloping downward, the feet at

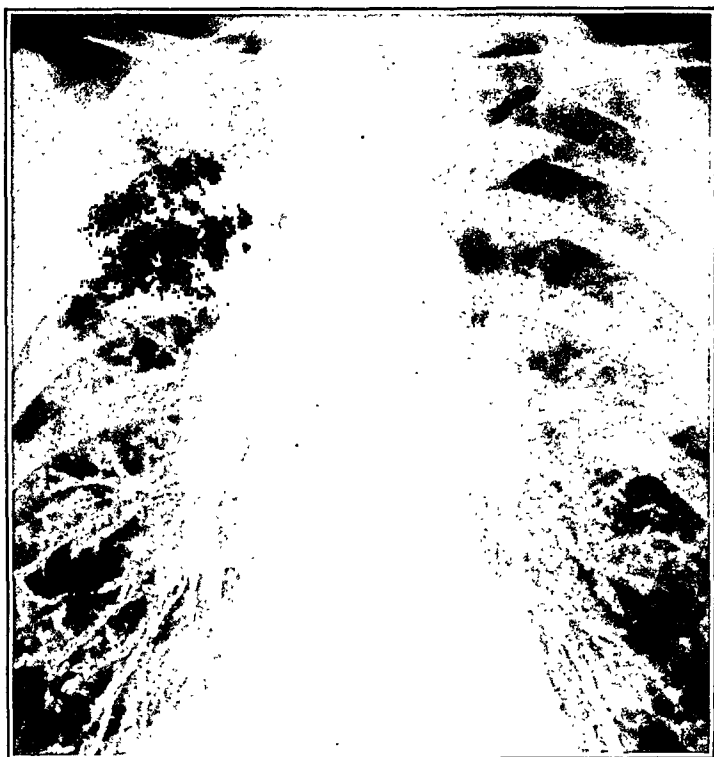


FIG. 1.—The lipiodol picture of chronic bronchitis, showing well-marked beading or varicosity of the bronchi, in certain places bladder-like dilatation of the alveoli, bronchiectatic cavity in the apex.

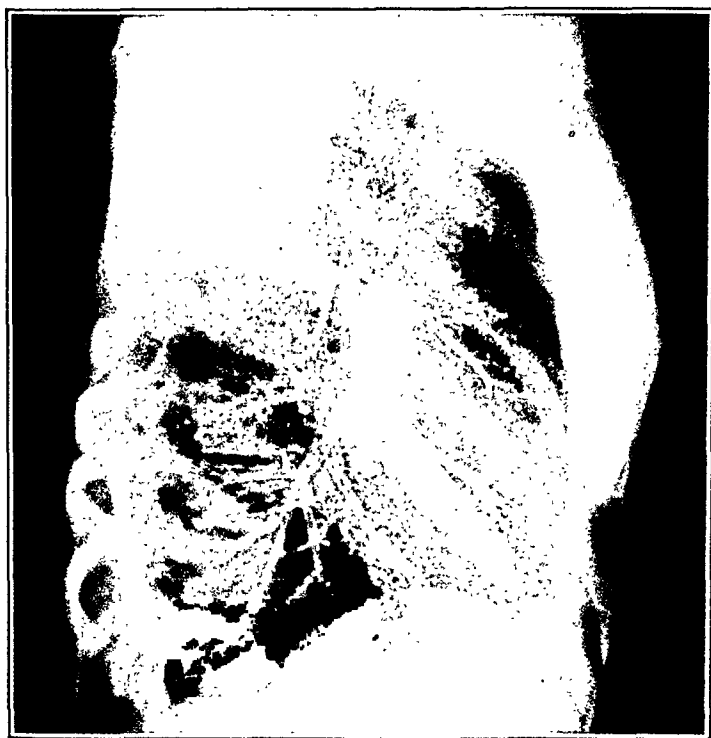


FIG. 2.—The lipiodol picture of asthma in the quiescent stage; some dilatation and varicosity of the larger bronchi, but chiefly a network of small bronchioles.



FIG. 3.—The lipiodol picture of "asthmatic" bronchitis, showing dilatation, varicosities, beading of the bronchi and bronchiectasis and network of fine dilated bronchioles.



FIG. 4.—The lipiodol picture of "emphysematous bronchitis," showing irregularity of the bronchi and entry of lipiodol into the alveoli.

an angle of 45 degrees, the patient is tilted 45 degrees head downward, lying on the same side for 3 or 4 minutes. A careful watch should be kept on the color of the patient, and the lipiodol should be introduced very slowly, the patient breathing with the mouth open and a little deeper than usual. The injection into the larynx of M vii of 5 per cent cocain is only sufficient to suspend the laryngeal cough reflex. I give adrenalin Mx, 1 to 1000 solution, which effectively abolishes the bronchial cough reflex.

The Radiographic Appearances. Simple chronic bronchitis may have no distinctive Roentgen picture, and that which is usually described is really the picture of combined chronic bronchitis and emphysema. Here the thorax is square and immobile, with rounded shoulders, obliquely-placed clavicle and plenty of space between the ribs; the heart is small, flattened and boot-shaped; the attachment of the pericardium to the vessels at the base of the lung prevents the emphysematous lung from flattening the heart completely. In the plain Roentgen film, the hilum and its contents are conspicuous, a well-marked and more or less vertical line bounding each side of the mediastinum. The heart may be enlarged and engorged from dilatation on its right side, or it may be small and smothered by the lungs. The diaphragm is flattened and the mediastina are encroached upon by the emphysematous lung. The whole lung substance has a mottled appearance due to dilated pulmonary vessels, and if the emphysema is well marked the dilated alveoli can be seen on the surface like diminutive bunches of grapes. The root shadows are exaggerated owing to congestion of the blood-vessels, and radiate toward the periphery of the lung. The whole of the ordinary Roentgen ray film of chronic bronchitis leaves much room for speculation and conjecture.

On the other hand, the radiograph of a chronic bronchitic lung injected with lipiodol leaves no room for speculation or any manner of doubt about the pathologic anatomy of the disease we are dealing with. The bronchial tree can be examined from the commencement of the trachea, and in emphysematous lungs the alveoli can be examined also. In most cases dilated beaded varicose bronchi are seen, chiefly in bronchi of the second to the fifth or sixth degree. This may be apparent in only a few isolated fusiform swellings or there may be general dilatation of most of the bronchi. It might be said that chronic bronchitis is the principal cause of bronchiectasis, were it not that bronchiectasis is the principal cause of the symptoms which are spoken of as chronic bronchitis. I do not suggest that bronchiectasis is never due to fibrosis dilating the bronchi from without, or to external pressure, but I am strongly of the opinion that the bronchial tubes are far more often dilated from within by the force of constant explosive coughing, such as whooping cough, acting, perhaps, on bronchi that are already weakened and relaxed as a result of physiologic dilatation due to sym-

pathetic nerve action. In the *chronic bronchitis* of hospital practice the bronchi, particularly the larger ones, are always dilated (Fig. 1).

The lipiodol picture in a so-called case of *bronchial asthma* is shown in Fig. 2. There is dilatation of the larger bronchi and of the smaller bronchioles. The result of frequent sympathetic action of the vagosympathetic complex of respiration is evident in irregularities of the caliber of the second to the seventh degree bronchi. This is the typical picture of a case of chronic bronchitis with frequent exacerbations of asthma. I do not know whether the dilatation is always permanent in these cases, but I believe that chronic bronchitis is not basically a disease, but a symptom of sympathetic nerve overaction. During an asthmatic attack the bronchioles are constricted and the lipiodol does not enter them, but between the attacks, or after the patient has had adrenalin, the characteristic network of small bronchioles is seen.

Fig. 3 shows the lipiodol picture of a case of "*asthmatic bronchitis*." There is a good deal of dilatation of the second to the seventh degree bronchial tubes, local or general irregularities in caliber, varicosities, beading and actual bronchiectasis. The irregularities dominate the picture, but the smaller bronchioles are also dilated, indicating disorder of the sympathetic portion of the vagosympathetic complex of respiration. The lipiodol has not entered the alveoli.

Fig. 4 shows the *emphysematous type of bronchitis*. There is an irregularity of the bronchi and lipiodol has entered the alveoli, which stand out like miniature clusters of grapes.

The Terminal Alveoli. Lipiodol does not enter the alveoli in the normal lung unless the patient coughs. The terminal bronchioles are, I believe, guarded by a sphincter-like development of their muscle. The sudden inspiratory effort which initiates a cough relaxes this muscle and allows the lipiodol to enter. When there is emphysema there is a permanent relaxation of this sphincter and permanent dilatation of the alveoli, so that the lipiodol can always enter. Lipiodol in the alveoli produces a typical gyrate pattern consisting of small punctate areas which look rather like a scarlatiniform rash. It is quite different from the irregular network, formed by the dilatation of the smallest bronchioles, seen in spasmodic asthma between the exacerbations and in many cases of chronic asthmatic bronchitis. The gyrate pattern is best seen if the radiograph is taken 24 hours after the injection. It is equally well seen a week later when the lipiodol has disappeared from the tubes but remains in the alveoli.

Conclusions. Since Laennec (1819) published the first clinical and pathologic account of chronic bronchitis little has been added to pathologic knowledge and diagnosis, and substantially nothing to effective treatment of the disease.

Bacteriology, which has relegated the anatomy and physiology of chronic bronchitis to the background appears not to be the fundamental cause of chronic bronchitis.

Knowledge of the autonomic nervous system (the only nervous supply of the lungs) has not been applied clinically to bronchitis, bronchiectasis, emphysema, nor to their relationship to asthma. Yet the system of living air channels is continuously changing in caliber, controlled by the action of the vagus and sympathetic nerves on the abundant musculature of the bronchi and bronchioles.

Lipiodol provides a wonderfully accurate method of studying the anatomic changes of the bronchial tubes during life and may be not only of therapeutic value in the four diseases mentioned but of still greater use in investigating the basal or fundamental cause of chronic bronchitis and its relation to asthma.

Asthma, chronic bronchitis, emphysema, and we may add bronchiectasis, are among the most difficult problems in medicine, their solutions depending not so much on cure as on prevention.

These four chronic diseases of the bronchial tubes need recasting and reconsidering in their relationship to the autonomic nervous system and their several relationships to each other.

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SPONTANEOUS HYPERVENTILATION TETANY.

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THE production of tetany in man by voluntary forced breathing was first described by Collip and Backus¹ in 1920. Grant and Goldman² working independently described similar experimental findings a few months later. The first clinical case of spontaneous hyperventilation tetany was described by Barker and Sprunt³ in 1922. The patient in this instance developed the condition following encephalitis. Since then a number of clinical instances have been described, but in most the development of the condition has been associated either with definite evidence of organic disease in the nervous system,⁴ as a hysterical manifestation, or in association with gastro-intestinal symptoms, such as abdominal pain and nausea.⁵

The cause of the tetany is generally accepted as due to an alkalosis resulting from loss of carbon dioxide from the blood. As a

result of this depletion a preponderance of basic substances accumulate in the blood and are excreted by the kidney, the urine becoming less acid. The ketonuria which is sometimes present is presumed to be produced by an interference with fat metabolism due to the alkalosis.

The case described below is of interest in that spontaneous hyperventilation developed in association with nausea, was rapidly followed by the onset of tetany with the production of marked ketonuria.

Case History. Miss H. R., aged 21, a medical student, was first seen at her home on December 18, at 10.30 A.M. She had noticed about 9.00 A.M. that her wrists were getting numb and stiff and that her hands were being drawn into a peculiar position. Shortly afterward her facial muscles became stiff and twitching of the muscles around the left eye developed. On examination she showed very marked hyperpnea, at a rate of 82 per minute. The arms were acutely flexed at the elbows and wrists. The hands were in the typical *main d'accoucheur* position with the three middle fingers fully extended and approximated and the thumb and little finger strongly adducted. The arms and fingers were very rigid on attempted movement. Trousseau's sign was present. The facial muscles were strongly contracted with the mouth drawn tightly so that the patient spoke with difficulty. Chvostek's sign could be elicited. There was slight rigidity of the legs. A diagnosis of spontaneous hyperventilation tetany was made and she was brought to the University Hospital at once. A specimen of venous blood was taken and she was given a 5 per cent mixture of carbon dioxid in oxygen through a close-fitting anesthetic mask. Within 2 or 3 minutes she stated that her hands were beginning to relax. The respiratory rate gradually slowed and the spasm diminished. She was quite relaxed and comfortable 8 minutes following the beginning of the administration of the gas. The specimen of blood taken at 11.00 A.M. 2 hours after the beginning of the attack, showed a carbon dioxid combining power of 37 volumes per cent.

Past History. She had had mumps, measles and scarlet fever in childhood. About 3 or 4 years ago she began to have occasional spells of nausea and vomiting accompanied by a dull pain in the lower abdomen. These attacks, she states, were followed by a feeling of air hunger which she relieved by taking deep breaths. Following these episodes the ends of her fingers would become numb, but there was no rigidity until the present attack. She had her appendix removed 7 months before her present admission following which there had been no further nausea and vomiting until 4 days before admission. She then suffered from nausea which was followed next day by a slight diarrhea. The latter readily responded to bismuth medication, but the nausea persisted and she feels that this may have been a factor in inducing deep breathing preceding her present attack of tetany.

On the day following admission to hospital she reported to the nurse that she was nauseated. At that time her respiration was normal. When the nurse returned to the room 2 or 3 minutes later the patient was breathing rapidly and showed severe tetany. Following the administration of 5 per cent carbon dioxid in oxygen for a few minutes the tetany disappeared.

A careful physical examination showed no abnormal physical signs except persistent absence of abdominal reflexes. The blood Wassermann reaction was negative and the blood count normal. The urine gave a positive Rothera test.

On December 20, an attempt was made to induce tetany by voluntary forced breathing. A control specimen of blood and a catheter specimen of

urine were taken, the bladder being completely emptied. At 11.1 A.M. the respiratory rate was 19, the pulse 72 and the blood pressure 125/68. At 11.16 A.M. voluntary forced breathing was begun. Three minutes later numbness developed in the hands and within a few seconds contraction showed in the fingers and facial muscles. Five minutes following the onset of hyperventilation the patient showed all the characteristics of severe tetany with carpopedal spasm, positive Chvostek and Trousseau signs. This condition was allowed to continue for 10 minutes. A second specimen of blood and a catheter specimen of urine were obtained. The respiratory rate was extremely rapid—102 per minute—the pulse rate was 80, the blood pressure 130/70. The patient who very intelligently coöperated during the experiment, was asked to breathe slowly. She was allowed to inhale a 5 per cent carbon dioxid oxygen mixture and within 15 minutes was completely relaxed and comfortable except for some muscular pain.

TABLE 1.—BLOOD AND URINE FINDINGS.

	Control period before forced breathing.	10 minutes after onset of tetany.
Plasma bicarbonate52 vols. per cent	.47 vols. per cent
Blood chlorids390 per cent	.410 per cent
Serum calcium	9.5 mg. per cent	10.1 mg. per cent
Blood pH	7.30	7.50
Urine pH	5.4	6.65
Urinary acetone bodies	Trace	Very heavy

Comment. The fall in blood bicarbonate, the increase in blood calcium and chlorids, and in blood and urine pH, are in keeping with the findings of other observers. The marked acetonuria has not, to our knowledge, been previously reported in this condition.

It may be noted here that the finding of hyperpnea, diminished plasma bicarbonate and acetonuria in a patient such as this might be mistaken for a condition of acidosis if the signs of tetany were not given a proper place in the picture.

In an attempt to exclude an hysterical element in the production of the chemical changes she was asked to hyperventilate, breathing a 5 per cent carbon dioxid mixture. On one occasion this was continued for 6 minutes and on another for 11 minutes without any signs of tetany appearing. While this finding does not exclude the possible hysterical origin of the overbreathing, yet it indicates that tetany could not be produced in the absence of a carbon dioxid deficit.

The blood chemical changes and the physiologic effects produced in the patient, make it evident that the condition is one of uncompensated carbon dioxid deficit. Due to the rapid shallow breathing, an abnormally great pulmonary carbon dioxid excretion has been produced. This has increased the ratio $\text{BHCO}_3:\text{H}_2\text{CO}_3$ and therefore the pH, and has resulted in the production of a condition of uncompensated alkalosis.

The exact nature of the acid base excretion in hyperventilation is not at all clear. Certain inferences may be drawn from the few instances in which serum electrolyte balances were studied. These

were carried out in 3 cases of prolonged overbreathing by Essen, Kauders and Porges,⁶ by Harrop and Loeb,⁷ and by Peters, Bulger, Eisenman and Lee.⁸ In all of these overbreathing was due to definite organic disease of the central nervous system. In the case reported by Harrop and Loeb compensation was quite incomplete and tetany was present. In the other 2 cases, while the patients had been overbreathing for a considerable period, neither tetany nor any disposition to develop signs of tetany was noticed. Acetonuria was not present. Blood studies in Peter's case confirmed the suggestion made by Essen and his associates that the bicarbonate deficiency was compensated for by an increase in the plasma chlorids. These workers had noticed that when the respiratory rate of their patient was normal, as it was during the night, the plasma CO_2 which had been high, moved in the opposite direction. There was then a reciprocal relationship between Cl^- and HCO_3^- . This change is presumed to be accomplished by a diffusion of chlorid anions out of the red blood corpuscles and probably also out of the tissue cells from the effects of the increased alkalinity of the blood on the Donnan equilibrium. The effect of such a chlorid redistribution would be to diminish the plasma alkalinity caused by the loss of carbonic acid and to lessen the tendency to tetany. This would explain the absence of tetany in the 2 last mentioned cases.

When this protective mechanism is impaired, as might be the case where the amount of blood chlorid is less than usual, as where vomiting is a symptom, milder degrees of overbreathing may be quite sufficient to cause alkalosis and tetany. This impairment might account for the observation made by McCance⁹ that certain individuals may be peculiarly susceptible to carbon dioxid deficit and develop tetany with scarcely noticeable overbreathing, and not as he suggests that it is due to an idiosyncrasy to slight blood changes. Experimentally it has been found that in the absence of organic nervous disease, signs of tetany rarely develop before 10 to 30 minutes of forced breathing, and even then one seldom sees such severe manifestations as our patient showed in 4 minutes. For this reason we feel that she probably shows the chlorid shift impairment that has been discussed.

Mild degrees of ketonuria have been reported by Adlersberg,¹⁰ and by Davies¹¹ and his associates in experimental studies on alkalosis. Peters and his coworkers have suggested that the absence of a chlorid increase with no alteration in base, in these cases, implies an increase in organic acids in the blood. They have suggested that the major part of this increase was due to lactic acid from the increased muscular activity occasioned by the tetanic spasms. The marked ketonuria and presumably the ketonemia present in this case implies that ketosis is one of the means by which the body attempts both to prevent alkalosis and to preserve osmotic equilibrium.

Summary. 1. A case of spontaneous hyperventilation tetany occurring in association with nausea has been described.

2. Following voluntary forced breathing, tetany developed in 3 minutes. After 10 minutes of tetany the blood showed a decrease in plasma bicarbonate, an increase in pH with a slight rise of calcium and chlorids. The urine showed an increase in pH and a marked ketonuria.

3. The rapid onset of tetany in this patient following increased breathing suggests that she may be peculiarly susceptible to carbon dioxid deficit leading to the production of tetany. The probable mechanism underlying this susceptibility and the cause of the over-breathing have been discussed.

(Our thanks are due to the patient who very kindly and intelligently coöperated.)

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DIRECT AND INDIRECT PNEUMOPERITONEUM INCIDENTAL TO ARTIFICIAL PNEUMOTHORAX.

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THE reason for presenting this report is to illustrate the two possible ways in which pneumoperitoneum may be produced when attempting to do artificial pneumothorax or following the introduction of air into the pleural cavity, namely, (1) by accidentally inserting the needle below instead of above the level of the diaphragm (direct pneumoperitoneum), and (2) by the passage of air from an established pneumothorax to the abdomen along one of the mediastinal structures which pass through the diaphragm (indirect pneu-

moperitoneum). We have seen 4 cases of this complication in the course of 5 years. Elrick¹ found only 11 cases reported by English and German authors up to 1929. Fishberg² reports 1 so-called direct pneumoperitoneum. Stefani and Desboeuf³ state that in their patient the air leaving the pleural space found its way to the peritoneal cavity through the hiatus for the esophagus or the aorta (indirect pneumoperitoneum).

The intensity of the symptoms depends upon the amount of air, position and sensitiveness of the patient, and the presence or absence of adhesions in the abdomen. We⁴ frequently observed while giving artificial pneumoperitoneum: (1) That there is usually no indication of abdominal or shoulder pain when less than 300 cc. of oxygen has been given; (2) that large amounts of oxygen may be given without discomfort in some instances, while others have complained of marked abdominal tension and shoulder pain following the inflation of comparatively small quantities of oxygen. The pain may be localized in the lower abdomen or on both sides of the chest. The sudden entrance of large amounts of air into the abdominal cavity may lead to nausea, vomiting, anxiety and difficulty in breathing.

The symptomatology and physical findings may be sufficient to establish the diagnosis. The condition may closely simulate spontaneous pneumothorax. However, the patient, contrary to the picture seen in spontaneous pneumothorax, is more comfortable in the supine than in the erect position. It is a good differential diagnostic sign that the tympanitic percussion sound detectable *above the liver in the upright or semireclining positions disappears* when the foot of the bed is elevated. The complete or partial symptomatic relief obtainable by this measure is also an evidence that freely movable air is present in the peritoneal cavity. Fluoroscopic examination and roentgenogram taken in the *upright position* will reveal the presence of air under one or both domes of the diaphragm. The roentgenogram taken in the Trendelenburg position will show the air in the pelvis and no air below the diaphragm in true pneumoperitoneum.

The manometer is not a reliable guide as to the entrance of the needle into the abdomen because its oscillations indicate negative pressure and follow the normal respiratory excursions at the sub-diaphragmatic region. Such was the case in 2 of our cases. This observation is in line with the findings of Overholt⁵ in animal experiments. Livingston⁶ explains the negativity in the upper peritoneal cavity by the proximity of the abdomen and thorax. He designates it as borrowed or reflected negativity; one which depends on conditions present within the thorax, not upon the abdomen itself. This negative pressure, says Binnie⁷ contrary to

what might be expected, is greater during inspiration than during expiration.

Case Reports. CASE 1.—R. H., moderately advanced pulmonary tuberculosis involving the upper two-thirds of the left lung. Artificial pneumothorax treatment began on January 9, 1932. The variations in the intrapleural pressure were from -10 to -6 (all manometric readings represent one-half of the true values) at the start and from -4 to -1 at the end of inflations during the first 9 treatments. From this time on, the initial and final pressures varied between -7 and -3 and $+2$ and $+8$, respectively. The roentgenogram taken on April 14, 1932, showed an 80 per cent collapse of the lower lobe and a 50 per cent collapse of the upper lobe, on the left side. The pneumothorax was discontinued because of adhesions on July 16, 1932. Roentgenogram taken in August, 1932, revealed a horizontal fluid level at the fourth interspace anteriorly, and a moderate collapse of both lobes of the left lung. Aspiration of the fluid and its replacement by air was attempted unsuccessfully. Continuation of the artificial pneumothorax was again decided because of positive sputum and persistent activity in the left lung and 500 cc. of air injected on October 1, 1932. The site of injection was the same as on previous inflations: the seventh interspace. The manometer registered -4 initial and 0 final pressure.

Patient felt some pain in the epigastric region while walking from the operating room to her bed (a distance of about 50 feet). Noticed more abdominal discomfort ("something moving") on the same afternoon. Pain at the appendix region and at the right shoulder appeared later on, particularly when she was sitting up. This was gradually getting worse and reached its maximum point about noon on the following day. At this time she appeared to be in great distress although she was not dyspneic or cyanotic. The acute discomfort gradually disappeared in 2 days. Roentgenogram (bedside) taken 48 hours after this inflation showed a partial pneumothorax on the left side, a heavy pleural band between the upper lobe and the chest wall, a homogeneous haziness, indicative of thickened pleura over the lower one-half on the left side, and free air under the right dome of the diaphragm. Roentgenogram taken in the *upright position* on October 6, 1932, showed a partial pneumothorax on the left side and large amounts of air under both domes of the diaphragm.

The pneumothorax treatment was continued. The patient related to us that whenever pneumothorax was being given she felt pain in the left shoulder and pressure in the left side of the chest (the treated side), then *while the air was being inflated she felt that "something snaps" or "something gives" in the epigastric region, followed by immediate relief from thoracic discomfort and shoulder pain.* The abdominal discomfort was noticeable after she got up from the operating table, but it was not as severe as on the first occasion.

Roentgenogram taken after the last treatment showed a partial pneumothorax on the left side and a pneumoperitoneum.

COMMENT. This is a typical instance of indirect pneumoperitoneum, in which the air found its way from an established pneumothorax to the peritoneal cavity alongside one of the mediastinal structures passing through the diaphragm.

CASE 2.—E. G., moderately advanced pulmonary tuberculosis involving the upper two-thirds of the left lung. Artificial pneumothorax treatment

from April 16 to July 9, 1932. The following data were recorded on the treatment card.

TABLE 1.—ARTIFICIAL PNEUMOTHORAX CASE 2.

	Date.	Amount introduced in cc.	Initial manometer.	Final readings.
1	April 16, 1932 . . .	500	-9	-3
2	April 23, 1932 . . .	300	-5	-3
3	April 30, 1932 . . .	500	-6	-3
4	May 7, 1932 . . .	300	-5	-3
5	May 14, 1932 . . .	100	-1	+2
6	May 21, 1932 . . .	400	-2	+3
7	May 28, 1932 . . .	400	-2	+3
8	June 4, 1932 . . .	500	-2	-1
9	June 11, 1932 . . .	500	-5	-3
10	June 18, 1932 . . .	500	-3	-2
11	June 25, 1932 . . .	500	-3	-2
12	July 9, 1932 . . .	200	-2	+2

Two hours after the 6th inflation patient started to complain of severe pain throughout the chest and in the upper part of the abdomen. She appeared very nervous and had difficult breathing during the next 24 hours; and nausea, vomiting and intense bilateral thoracic pain on the second day following this inflation. Roentgenogram taken on same date revealed free air under both domes of the diaphragm.

COMMENT. Indirect (delayed) pneumoperitoneum was produced by forcing air from a positive pressure (high tension) pneumothorax into the peritoneal cavity through one of the diaphragmatic openings, in a case in which 5 successful inflations preceded, and 6 regular pneumothorax treatments followed, the incidental pneumoperitoneum.

CASE 3.—B. G., moderately advanced pulmonary tuberculosis. Artificial pneumothorax began on August 27, 1931, and 29 inflations given. The smallest amount of air was 350 cc., the largest 850 cc. The initial intrapleural pressure varied between -8 and -3; the final pressure registered from -3 to -1, with the exception of the 12th inflation when the final manometer reading was 0. The amount of air injected was 650 cc. on this occasion. The patient stated that this twelfth treatment felt "different" from the previous ones. She complained of severe chest pain immediately following inflation; the pain persisted for 24 hours. The fluoroscopic examination and the roentgenogram taken directly after treatment revealed no pneumothorax but the presence of air under both domes of the diaphragm. The next inflation 5 days later produced a fair pulmonary collapse. No pneumoperitoneum was found after the absorption of air injected into the abdomen at the 12th treatment.

COMMENT. An obvious case of direct pneumoperitoneum.

CASE 4.—M. B., far advanced pulmonary tuberculosis involving the upper and lower one-thirds of the right lung and the entire extent of the left lung. Exeresis of the left phrenic nerve was performed on April 2, 1931. Because of a massive hemorrhage, artificial pneumothorax was attempted on the left side, with the following results.

TABLE 2.—ARTIFICIAL PNEUMOTHORAX CASE 4.

	Date.	Amount introduced in cc.	Initial manometer.	Final readings.
1	June 4, 1931 . . .	100	-5	-1
2	June 5, 1931 . . .	500	-4	+2
3	June 13, 1931 . . .	800	-6	0
4	June 17, 1931	(pleural shock)	
5	June 27, 1931 . . .	100	-5	+7
6	Sept. 19, 1931 . . .	350	-2	-1
7	Sept. 21, 1931 . . .	600	-2	+2
8	Sept. 24, 1931 . . .	300	-2	+9
9	Sept. 30, 1931 . . .	1000	-5	-1
10	Oct. 3, 1931 . . .	800	-3	- $\frac{1}{2}$
11	Oct. 7, 1931 . . .	500	-2	- $\frac{3}{4}$

Following the inflation, patient complained of severe pain on the left side of face and neck. Treatments discontinued in June because of adhesions. Artificial pneumothorax was again begun in September because of the increasing size of a cavity on the left side. The level of the left dome of the diaphragm was two finger-breadths higher than that of the right. The inflations were continued with similar amounts and manometer readings until December, 1932. The only exception was the 38th treatment (June 11, 1932), when the initial pressure of -2 rose to +12 following the injection of 150 cc. of air. Then the needle was carried deeper, whereupon the manometer showed -6. The final manometer reading was -3, following the injection of additional 600 cc. of air.

COMMENT. This patient was given pneumothorax and direct pneumoperitoneum on different occasions, and a high tension air pocket and a direct pneumoperitoneum were established in one session on June 11, 1932. The roentgenogram taken on October 28, 1931, showed a small pneumothorax directly above the left diaphragm and a very large pneumoperitoneum.

Summary. 1. Pneumoperitoneum is a very rare complication of artificial pneumothorax.

2. Two cases of direct pneumoperitoneum are presented. It occurs when the pneumothorax needle is inserted below, instead of above the diaphragm.

3. Our manometer readings indicate that the subdiaphragmatic intraabdominal pressure is negative and that it oscillates parallel with the intrapleural pressure changes.

4. Two cases of indirect pneumoperitoneum are recorded. It is concluded, from the study of symptoms and roentgenologic findings, that in these cases the air found its way from an established pneumothorax into the peritoneal cavity along the structures passing through the diaphragm.

5. The best means for establishing the diagnosis is the roentgenogram taken in the upright position.

6. Immediate symptomatic relief can be obtained by elevating the foot of the bed, thus shifting the air from below the diaphragm to the pelvis.

7. Proper orientation as to the position of the diaphragm in relation to the site of injection and avoiding the forcing of air under high pressure will aid in preventing the occurrence of accidental pneumoperitoneum.

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ELECTROMYOGRAPHIC RECORDS OF MUSCLE TREMORS AND PHONOMYOGRAPHIC RECORDS OF MUSCLE MURMURS IN POSTENCEPHALITIC PARKINSON'S DISEASE AND ESSENTIAL TREMOR.*

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It is a generally accepted teaching of physiology that when a muscle contracts, an electric current is generated. When one of the larger voluntary muscles contracts, a sound is produced. This may be demonstrated easily by voluntarily contracting the biceps or triceps muscle and listening with the stethoscope; a rather loud, continuous, crackling and rumbling sound is audible. Muscle

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FIG. 1.—Phonomyogram. Record taken from left trapezius muscle of a man with postencephalitic Parkinson's disease. The time marker below records 1/100 second.



FIG. 2.—Phonomyogram. Continuation of record shown in Fig. 1. The line which traverses the upper part of the figure records the tremor of the right index finger. The record was obtained by fastening a straight piece of rather heavy wire to the finger, the subject holding the wire vertically before the camera. The line is composed of a series of shallow oscillations corresponding almost exactly in number each second to the record obtained from the trapezius muscle. The rate is the same as and synchronous with that of the trapezius muscle. The time marker below records 1/100 second.

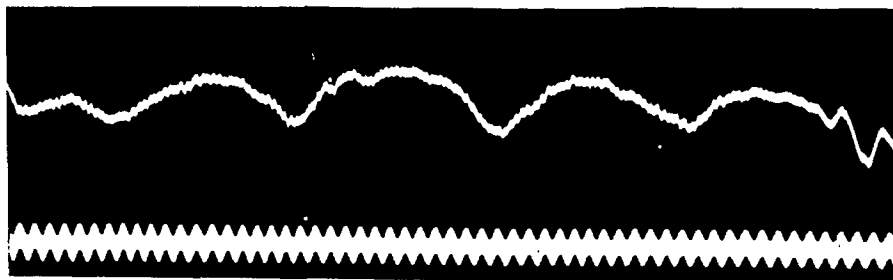


FIG. 3.—Phonomyogram. Record taken from the right trapezius muscle of a woman with an essential tremor. The time marker below records 1/100 second.

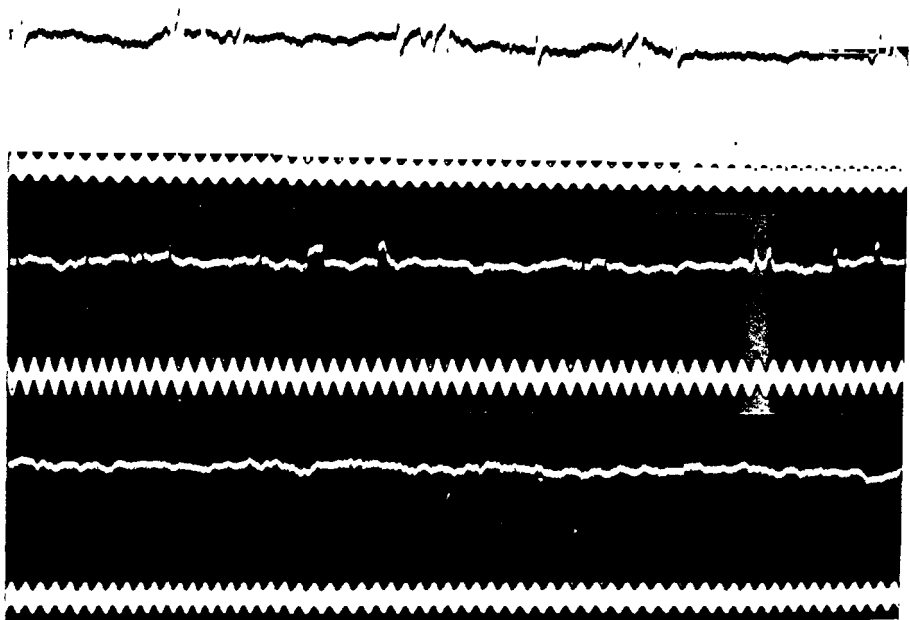


FIG. 4.—Electromyogram. Record taken from left trapezius muscle of a man with postencephalitic Parkinson's disease. Uppermost record obtained by inserting Adrian-Bronk needle deep into the trapezius muscle. The intervals of deflection correspond fairly closely with the intervals between peaks of the phonomyogram. For the record in the middle position, the needle was inserted superficially into the muscles; the deflections occur at irregular intervals and are insignificant. When the lowermost record was made the needle was not in the muscle, but in the subcutaneous tissue; deflections are absent. The time marker below records 1/100 second.

sounds or muscle murmurs may be heard over the thorax of persons who are extremely nervous or who are cold, especially if they are chilled enough to shiver. The sounds are rhythmic and low in pitch, and vary considerably in intensity and frequency of occurrence. They vary in number from 200 to several hundred a minute. Furthermore, they are not constant, and are greatly influenced by inspiration and expiration. These facts are well known. Wartenberg has recently described how muscle sounds, produced by contracting the masseter and orbicularis oculi muscles, may be heard by placing the head in a pillow and forcibly contracting these muscles.

We have studied muscle murmurs in 8 cases of postencephalitic Parkinson's disease and in 1 case of essential tremor. The murmurs in the cases of Parkinson's disease occurred rhythmically, and at the rate of 300 to 400 a minute, the average being about 350 each minute. In quality the murmurs often resembled the sound of an engine in a tunnel or that of a motor boat. In some instances they were similar to fetal heart sounds.

The murmurs could be heard over the body and the extremities, and could be detected by the unaided ear. They were heard most plainly over the thorax, and were loudest over its posterior portion, that is, over the trapezius and latissimus dorsi muscles. They were similar to the sounds heard when examining nervous or cold persons, but they were louder and much more striking in character. The sounds varied somewhat as the degree of tremor varied, but they could be heard when the tremors could neither be seen nor felt.

That a resting muscle will produce no sound is generally accepted. It is believed that the muscle murmurs and sounds which we are reporting are due to muscles which are held in a state of extreme tautness, and that a few fibers, varying in number, are contracting somewhat rhythmically to produce the sounds.

Fig. 1 is a reproduction of a phonomyogram obtained by placing a suitable microphone over the trapezius muscle of a man with postencephalitic Parkinson's disease. The induced currents set up in the microphone were carried to an amplifier employing resistance capacity coupling, and thence to the Matthews oscillograph. The movements of the iron tongue of the oscillograph were recorded on the rapidly moving photographic paper of the camera. Accurate timing was obtained by photography of the movements of a tuning fork having 100 vibrations a second.

Fig. 2 is a reproduction of another portion of the phonomyogram shown in Fig. 1.

A portion of the phonomyographic record of a person with essential tremor and mild hyperthyroidism is shown in Fig. 3. In this case the muscle sounds were not as pronounced nor as constant as in the case of postencephalitic Parkinson's disease (Figs. 1 and 2), and voluntary movements and respiration apparently exerted a

daily. When a patient's appetite decreased, which invariably happened, he was instructed to eat all of his diet under the penalty of not being allowed whiskey the following day. In this manner the caloric intake was kept at 3500 or more calories per day. After the lesions healed the patients were no longer given whiskey. They remained in the hospital, however, under observation for several weeks and were discharged with a severe warning as to the dangers of further drinking.

Observations. It can be seen (Table 1) that 62 of the 73 cases studied had a history of severe alcoholism, 6 denied alcoholism, and no information was obtained from the remaining 5 concerning the use of alcoholic beverages. Two of the 6 denying the use of alcohol developed pellagrous lesions secondary to carcinoma of the stomach, and a third developed the changes of pellagra while receiving a restricted diet used in the treatment of peptic ulcer. It is noteworthy that the alcoholism occurred from such diverse materials as "canned heat," "white mule," "raisin jack," "wood alcohol," and "hooch."

TABLE 1.—PELLAGRA: ANALYSIS OF 73 CASES.

Race and sex.	No. of cases.	Av. age.	Alcohol (?)	Diarrhea.	Dementia.	Stomatitis.	Anemia.	Died.	Autopsy.
White males . . .	28	50	Yes 25 No 3 N.D. 0	Yes 17 No 8 N.D. 3	Yes 8 No 19 N.D. 1	Yes 24 No 4 N.D. 0	Yes 7 No 21 N.D. 0	10	7
White females . . .	7	42	Yes 6 No 1 N.D. 0	Yes 5 No 1 N.D. 1	Yes 3 No 2 N.D. 2	Yes 5 No 0 N.D. 2	Yes 2 No 3 N.D. 2	5	0
Black males . . .	10	36	Yes 9 No 0 N.D. 1	Yes 7 No 2 N.D. 1	Yes 7 No 3 N.D. 0	Yes 8 No 0 N.D. 1	Yes 3 No 5 N.D. 2	7	6
Black females . . .	28	31	Yes 22 No 2 N.D. 4	Yes 19 No 6 N.D. 3	Yes 23 No 3 N.D. 2	Yes 27 No 1 N.D. 0	Yes 12 No 14 N.D. 2	17	10
Totals . . .	73	40	Yes 62 No 6 N.D. 5	Yes 48 No 17 N.D. 8	Yes 41 No 27 N.D. 5	Yes 64 No 6 N.D. 3	Yes 24 No 23 N.D. 6	39	23

N.D. = No data.

From Fig. 1 we observe that the admissions of pellagra patients increased in the summer and fall in the manner previously described for the endemic disease.⁸

The 10 patients who received an adequate diet, yeast, and large quantities of whiskey recovered with apparently no ill effects. Their skin lesions and the stomatitis improved rapidly. Eight of the 10 pellagrins developed symptoms of peripheral neuritis subsequent to their admission to the hospital. (This is in keeping with the usual development of this type of neuritis after the other manifestations of the disease have improved.)

Discussion. It is generally agreed that the pellagra found in the North is usually associated with severe alcoholism. The present study, which is probably representative of any northern city, demonstrates that over 90 per cent of our patients developed the lesions of pellagra following excessive drinking. Nearly all of these patients gave a definite history of loss of appetite followed by the substitution of whiskey for food, thus strongly suggesting that the food intake was not sufficient for adequate nutrition. It follows that there is a very close relationship between alcoholism and so-called alcoholic pellagra. We have shown in this experiment that

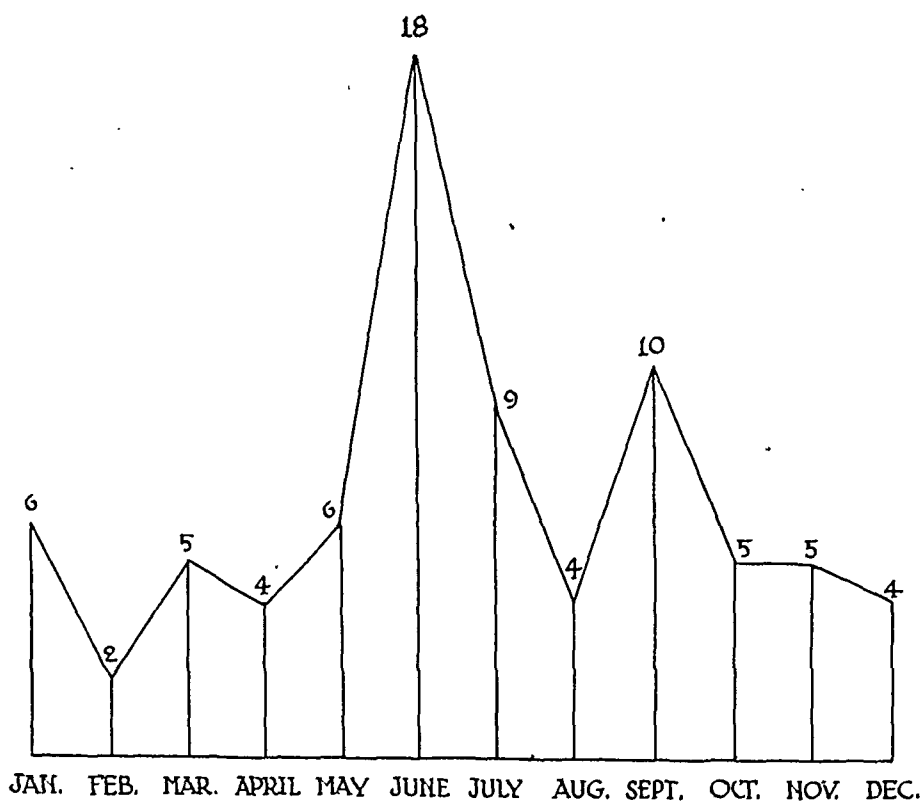


FIG. 1.—Admissions by months of the 73 pellagrins.

these patients before hospitalization drink large quantities of alcoholic beverages, eat little or no food, and yet they can be cured even when given large amounts of whiskey if an adequate diet is ingested.

The alcoholic type of pellagra has been previously recognized^{8,9,10} and writers have speculated freely concerning its relationship to the non-alcoholic (endemic) type. On theoretical grounds it may be considered that the whiskey predisposes to the development of pellagra by either destroying the so-called pellagra preventive factor or by altering the gastro-intestinal tract so that it becomes incapable

of assimilating the preventive substance. Likewise it has been suggested on theoretical grounds that foreign substances in the whiskey, such as the higher alcohols, produce the lesions of pellagra.

A consideration of the kinds of alcoholic beverages taken by the patients in this series indicates that it would be difficult to determine whether or not deleterious substances were present in the liquors which predisposed to the development of the disease. It appears unlikely to us, however, that any specific deleterious material would be present in the many kinds of beverages taken. The present observations show that the consumption of large quantities of whiskey at the same time that an adequate diet was received did not interfere with the clinical improvement of the patients. This is strong evidence that alcohol does not directly inactivate either all the gastric secretion or all the potent substances in the food. While it is conceivable that imbibing alcoholic beverages may in some manner affect either the food or gastric secretion so that a quantitative loss of important material occurs, it seems unlikely that this is sufficient to explain the development of the disease.

It is well known that many individuals drink large quantities of alcoholic beverages for years without suffering from loss of appetite, vomiting or pellagra. Correlation of these findings logically suggests the following hypothesis: Severe alcoholic imbibition by some individuals causes inadequate food ingestion by decreasing the appetite and often precipitates nausea and vomiting. This predisposes to the development of pellagra because the person no longer receives an adequate diet, but utilizes the calories in the alcohol.

This study indicates that pellagra following severe alcoholism should be considered the same disease entity as endemic pellagra, since characteristically both diseases have a predisposing dietary lack, the same seasonal occurrence (Fig. 1), the same symptomatology (Table 1), and the same lesions.

Summary and Conclusions. 1. It has been shown in this investigation that over 90 per cent of the patients with pellagra developed it following severe alcoholism. This incidence is probably representative of any northern city.

2. We have demonstrated that pellagra patients recover following the simultaneous administration of large quantities of corn whiskey, an adequate diet, and yeast.

3. Our observations suggest that the relationship of alcoholism to the development of pellagra is that the usual afflicted individual (pellagrin) loses his appetite and substitutes drink for food, thus favoring the production of pellagra.

4. Facts are advanced which support the hypothesis that alcoholic pellagra is a form of true (endemic) pellagra.

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THE CLINICAL PICTURE OF BROMID POISONING.

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THE picture of bromid intoxication, particularly that of the delirium state, is often modified and colored, as Diethelm¹ points out, by the underlying psychiatric make-up of the individual. Certainly, this must be true in those institutions caring largely for psychiatric patients. Wagner and Bunbury² observed that the patient suffering from bromid intoxication is most often of a type which takes refuge in drugs and alcohol from conditions considered intolerable. Nevertheless, in a general hospital, one not infrequently meets with cases of "pure," or almost "pure," bromid delirium in which, after the elimination of the exciting drug, there are surprisingly few abnormalities remaining. The taking of the drug is often accidental so far as the patient is concerned. It is not uncommonly prescribed during acute illnesses or during convalescence from acute illnesses. And, of course, in a large group of patients, it is taken in the form of "patent" medicines during a time of unusual physical or mental distress. The normality of many of these patients after the delirium has cleared is in startling contrast to their condition during the stage of the stupor or delirium.

Diethelm¹ states that he is unable to find any symptoms charac-

teristic of bromid delirium and, further, that the "clearing up of the mental picture is not always parallel to the diminution of the bromid content." In the small series of cases reported here, the opposite seems to be true, although the limited material prevents speaking with certainty. It seems altogether probable that the clinical characteristics of any given series of cases will be modified largely by the type of institution in which the cases occurred. The cases reported here were admitted to the general wards for a variety of medical and surgical reasons. Some of them unquestionably fall into the class described by Diethelm,¹ Wagner and Bunbury,² Zondek and Bier,³ *et al.*

In those cases in which adequate study was made of the blood and spinal fluid halids, there is an apparent relationship between the clinical condition of the patient and the blood and spinal fluid halid levels. While the number of cases and determinations in the individual case are not as large as one could wish, the results presented are at least suggestive and point the way toward more complete studies, which are being carried out at the present time with the electrometric titration method of Hastings and van Dyke.¹¹

Report of a Case: (No. 19,488).—White male, aged 17, admitted October 28, 1932, in a deep stupor. Five weeks previously patient had "bad cold" accompanied by headache and "nervousness." One week later he complained of jerking of muscles of legs and face. He was given bromids by his local physician. After several days in bed, during which time he was afebrile, the muscle twitching disappeared, but the patient grew drowsy and unresponsive. The family, accordingly, increased his medicine dosage. The stupor deepened, maniacal attacks ensued, and the patient was brought into the hospital because he could not be controlled at home.

He was a normally developed young white male, stuporous and dehydrated. Temperature was 37.5° C. Pulse rate 108. During the examination there were frequent myoclonic movements of the extremities and facial grimacings. The pupils were widely dilated but reacted normally to light. The disks were clearly outlined. There were moderate dough-like rigidity of the arms and legs and markedly hyperactive tendon reflexes. There was no clonus, however, and the Babinski and Kernig's signs were negative. The neck was slightly stiff. The abdominal reflexes were not obtained, but the cremasterics were present.

Lumbar puncture revealed a water-clear spinal fluid containing 10 lymphocytes per c.mm. The Pandy test was one positive. The sugar content was 55 mg. per cent. The bromid and chlorid findings are shown in Chart I.

During the next 4 days the patient was completely unmanageable. He had almost constant auditory and visual hallucinations, usually of a frightening nature, and required constant restraint. In his less maniacal moments he told wildly circumstantial stories of being pursued by animals, by men with guns, etc. Large doses of chloral hydrate, paraldehyde, and sodium amytal were not only ineffective but rather augmented his delirium. Fluids and large quantities of sodium chlorid were given by mouth whenever possible, and hypodermoclyses and intravenous injections of 5 per cent glucose in physiologic saline were resorted to frequently in order to maintain a fluid intake of 6000 to 7000 cc. daily.

Four days after admission, lumbar puncture was repeated and 40 cc.

spinal fluid removed. Physiologic saline was given intravenously (750 cc.), and 10 minutes later an additional 20 cc. of spinal fluid were removed. Analyses of the 2 specimens showed an apparent increase in total protein only (0.064 to 0.08). The second specimen showed Cl., 102.9 mM/L (602 mg. per cent); Br., 17.4 mM/L (180 mg. per cent; replacement of 14.4 per cent); sugar, 70 mg. per cent; total protein, 0.080 gm. per cent. For the findings of the first specimen and simultaneous blood analysis see Chart I.

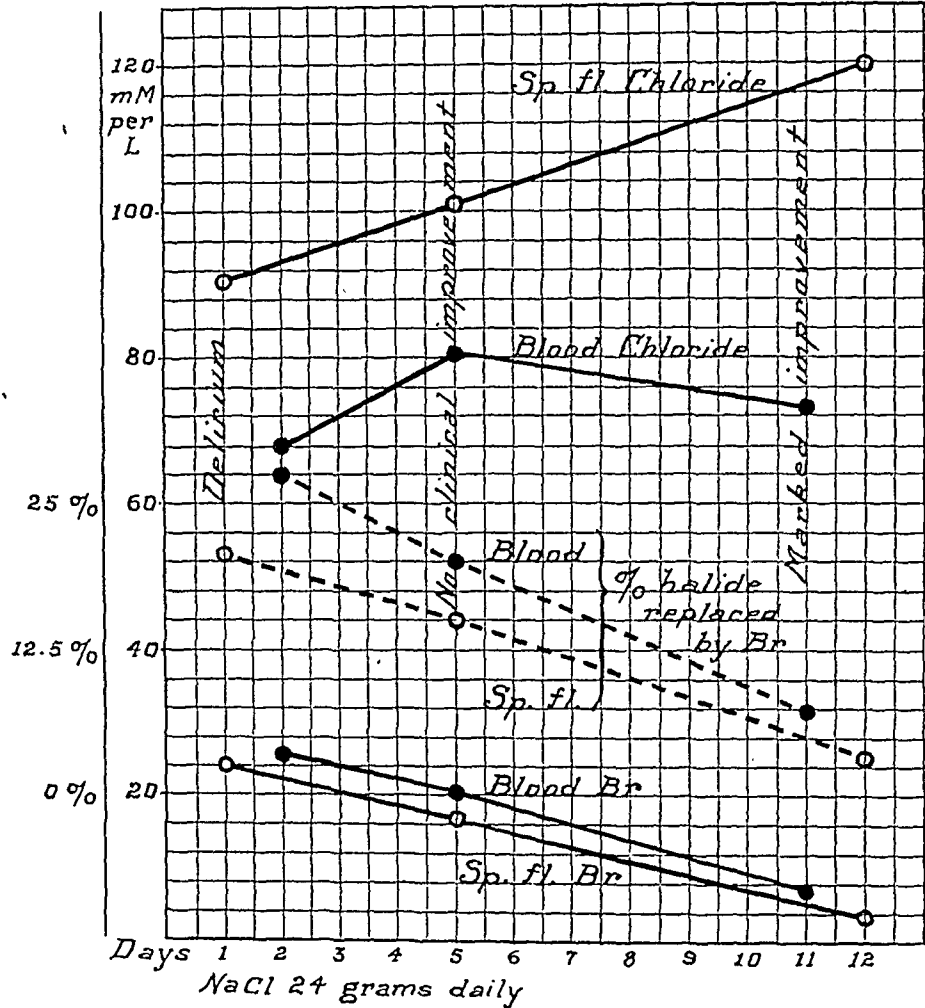


Chart I
Clinical examination of blood and spinal fluid (Case 1).

On the 8th and 9th days after admission the patient was fairly lucid at intervals, but his delirium continued at night. On the morning of the 10th day he dramatically announced that he was well and fully recovered. He was well oriented, smiling and mentally alert. He remembered the preceding weeks as a hideous "nightmare" and showed some concern about the possibility of a return of the alarming experiences. For the blood and spinal fluid bromids and chlorids at recovery see Chart I. The sugar content of spinal fluid was 65 mg. per cent; total protein, 0.088 gm. per cent. From the 10th to the 12th day the patient was fully rational and suffered nothing worse than a few "bad dreams." After the 12th day there were

no further symptoms. At discharge on December 16, 1932, there were no discoverable abnormalities. The pupils were normal in size. The tendon reflexes were normally active, and the abdominal reflexes were lively.

Symptoms. In this series there were 8 cases in which the symptoms were apparently the result of bromid poisoning alone without confusing psychiatric basis. A composite picture of these typical cases is as follows: an individual with one or a variety of medical or surgical (somatic) complaints, has taken bromids during a period of days or weeks. After a variable length of time the patient becomes restless, irritable and emotionally labile, and complains of headache, blurring of vision, interrupted sleep and disordered, usually frightening dreams. As these symptoms endure there are observed weakness, ataxia, slurring and hesitancy of speech, irrelevant conversation, poor appetite, and loss of memory, particularly for recent events. Drowsiness and lethargy are soon followed by stupor, and sleep is even more disturbed by disordered dreams. Hallucinations, both visual and auditory, become a prominent feature, and maniacal attacks of excitement are provoked by the fear reaction produced.

The patient does not appear acutely ill. The facies are expressionless (McFadden⁴) and vacuous. The temperature and respiratory rate are not elevated, although there may be a moderate tachycardia. The leukocytes are within a normal range or only slightly elevated. The patient is disoriented and stuporous, although capable of being aroused to answer questions in a seemingly intelligent fashion. He exhibits fabrication and confabulation and has many delusions concerning himself and those about him. Most of the delusions, often of persecution, seem to be secondary to his own hallucinatory experiences. Unless his attention is forcibly held, he sinks back into stupor.

The skin and mucous membranes are dry and the tongue is furred. There is no rash (7 cases) and no general lymph glandular enlargement. The neck is not stiff (7 cases) and Kernig's sign is negative (8 cases). The pupils are widely dilated (7 of 7 tested cases), but react fairly promptly to light, both directly and consensually. Convergence is poor, diplopia is present (7 of 7 tested cases), so that contraction during accommodation cannot be tested (although Case 1 had lost the accommodation reflex even though good convergence without diplopia was secured). The optic disks show no papilledema. There is no weakness, *per se*, of the muscle groups, but there are marked ataxia and incoördination. The reflexes are strongly *hyperactive* (6 of 7 tested cases), but the accessory signs of upper motor neurone disturbance are conspicuously absent. The abdominal reflexes are not obtained (5 of 5 tested cases). For summary of important signs and symptoms see Table 1.

Treatment. We have found that the usual sedatives and hypnotics not only do not allay the excitement but rather seem to

TABLE 1.—SUMMARY OF DATA OF 1 TO 8 CASES.

Case No. Age, race, sex	Condition (other than bromism)	Restlessness, irritability	Headache	Blurring of vision	Sturring speech	Memory loss	Weakness	Ataxia	Lethargy	Vacuous facies	Disorientation	Hallucinations	Dehydration	Stiff neck	Kernig's sign	Dilatation of pupils	Hyperactive reflexes	Babinski	Ankle clonus	Abdominal reflexes	Leukoocytes in blood (thousands per c.mm.)	Spinal fluid
21503 21, W ♀	Influenza	++	+	++	++	++	++	++	++	+	+	++	++	Slight	○	+	+	○	○	Not tested	8.8	○
19488 17, W ♂	"Bad cold" (chorea?)	++	+	++	++	++	++	++	++	+	+	++	++	○	○	+	+	○	○	○	5.8	+
13580 24, W ♀	Epilepsy	++	+	++	++	++	++	++	++	+	+	++	++	○	○	+	+	○	○	○	4.5	○
20899 24, W ♀	Mastoiditis (?)	++	+	++	++	++	++	++	++	+	+	++	++	○	○	+	+	○	○	○	11	○
3548 24, W ♀	"Nervous- ness"	++	+	++	++	++	++	++	++	Not noted	+	++	++	○	○	+	+	○	○	○	6	
13869 36, W ♀	Postopera- tive	Not observed	+	Not observed	++	++	++	++	++	Not noted	+	++	Not noted	○	○	Not noted	Not tested	Not tested	Not tested	Not tested	8.4	
4260 15, W ♀	Pregnancy (?)	++	+	++	++	++	++	++	++	+	+	++	++	○	○	+	+	○	○	Not tested	11	○
751 55, W ♀	Hyperten- sion	++	+	++	++	++	++	++	++	Not noted	+	++	++	○	○	+	+	○	○	○	9.9	

increase the number and intensity of the hallucinations. The administration of luminal, barbital, chloral hydrate, paraldehyde, sodium amytal, etc., was invariably followed in a short time by maniacal outbursts. Even sodium amytal given intravenously up to 0.4 gm. had no effect in quieting the 2 patients in which it was used.

Isolation from noise and from all disturbance, together with hydrotherapy, is most effective when it can be secured.

In accordance with the experience of Wile,⁵ Wuth,⁶ Harris and Hauser,⁷ Diethelm,¹ McFadden,⁴ *et al.*, sodium chlorid up to 2 gm. every 2 hours is given by mouth. A daily intake of 6000 to 8000 cc. of fluid is secured, if necessary by parenteral administration of physiologic saline and of 5 per cent glucose solution.

We are unable to confirm the experience of Wagner and Bunbury² that soon after the administration of sodium chlorid there is a rise in the blood bromid, concomitant with an increase in the severity of the symptoms. It may be that our determinations were made too long (usually 3 days) after the beginning of treatment. After 3 days of treatment the bromid content of the blood and spinal fluid was always lower, and considerably lower, than the pre-treatment level. We did not observe any exacerbation of symptoms after beginning of treatment.

Our own figures are in accord with the experimental results of Palmer and Clarke,⁸ who found that after the intravenous administration of NaCl the blood bromid level decreases along with a greatly increased urinary excretion of bromid. They point out, further, that chlorid administration not only increases the total halid excretion but increases the fraction of bromid in it. Thus the actual rate of bromid elimination is enhanced by increasing the chlorid intake.

Usually during the first 5 days of treatment little clinical improvement was detected. Disorientation, hallucinations, delusions, confabulation, and speech defect persisted. Slight remissions often occurred in the early morning hours with exacerbations toward afternoon and evening. Between the 6th and 9th days there was often an abrupt change, the patient becoming completely lucid and oriented during the day but with disordered dreams at night for several days more. Treatment was always continued until the patients were symptom free.

Chemistry. A modification of the Wuth method⁶ was used for the determination of bromid. The determinations were made on whole blood instead of serum. Standards of known bromid content were made up, and the value of the unknown blood was read off directly on the colorimeter.

Although definite conclusions cannot be drawn from the material presented, the following values may be significant:

1. Active delirium occurred in patients with a blood bromid content of from 25 millimols per liter in Case 2 to 9.7 mM/L in Case 7,

and the delirium state continued even when the bromid content had fallen to between 20 mM/L in Case 2 and 9.2 mM/L in Case 1.

2. The figures for spinal fluid corresponding with the above values for blood are: (a) Delirium level: 24.2 mM/L Case 2 to 10.8 mM/L in Case 1. (b) Delirium continued with values between 17.6 mM/L in Case 2 and 6.6 mM/L in Case 1.

3. Definite clinical improvement (orientation, loss of hallucinations and delusions, return of reflexes and pupils to a normal state of reactivity) occurred when the blood bromid level had fallen to between 5.2 mM/L in Case 3 and 5.8 mM/L in Case 2, and the level in the spinal fluid had reached 2.7 mM/L in Case 1 to 3.8 mM/L in Cases 2 and 3. (See Table 2.)

TABLE 2.

Case No.	Day.	Condition.	Blood halids (mM/L).			Spinal fluid halids (mM/L).		
			Br.	Cl.	Per cent halid replaced by Br.	Br.	Cl.	Per cent halid replaced by Br.
1	Admission	11.1	68.0	14.0	10.8	94.0	10.3
	4th	No improvement	9.2	99.0	8.5	6.6	109.0	5.7
	8th	Clinical improvement	5.6	92.0	5.7	2.7	123.0	2.1
2	Admission	25.0	67.5	27.0	24.2	90.6	21.0
	3d	No improvement	20.0	80.0	20.0	17.6	101.0	14.8
	10th	Clinical improvement	5.8	74.0	7.2	3.8	119.6	3.0
3	Admission	17.4	54.6	24.0	15.5	92.8	14.3
	3d	No improvement	10.0	76.0	11.6	7.3	112.0	6.1
	6th	Clinical improvement	5.2	77.4	6.2	3.8	120.0	3.0
	9th		4.4	84.2	4.9	3.4	122.0	2.7
4	Admission	19.0*					
	12th	No improvement	13.9†					
	21st‡	Discharged well						
5	Admission	10.0					
	13th	Discharged well	2.1	104.0	1.8			
6	Admission	12.0					
	5th	No improvement	7.0	68.0	9.3§			
7	Admission	9.7	89.0	9.8			
	6th	Discharged well	4.0	96.0	4.0			
8	Admission†						
	2d	No improvement	9.7	81.0	10.6			
	8th‡	Discharged well						

* Not treated.

† Treatment begun.

‡ No blood or sp. fl. studies.

§ Discharged against advice.

It will be noted that the spinal fluid bromid levels are uniformly lower than the blood bromid levels.

This result agrees with that of Malamud, Fuchs, and Malamud,⁹ who used the colorimetric method, and with the recently published figures of Mishkis, Ritchie, and Hastings,¹⁰ using the more accurate electrometric titration method previously described by Hastings and van Dyke.¹¹

Summary. 1. There is presented a group of patients suffering from bromid intoxication in which certain signs and symptoms recurred with sufficient regularity to constitute a clinical syndrome.*

2. The psychiatric make-up of this group is contrasted with the type of cases reported elsewhere.

3. The effect, both clinical and chemical, of specific treatment with sodium chlorid is discussed.

4. It is suggested that a distinct parallelism exists between the bromid levels in the blood and spinal fluid and the clinical condition of the patient. It seems probable that an even closer relationship may be found between the clinical condition and the percentage of the total halid replaced by bromid.

My thanks are due to Dr. W. A. Perlzweig and the members of his Department for the chemical studies and to Miss Elizabeth Brodel for the preparation of the charts.

* Since the inception of this paper we have been able to recognize from the signs and symptoms alone 3 additional cases of bromid poisoning.

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CALCIUM AND PHOSPHORUS METABOLISM OF AN OSTEOMALACIA PATIENT, A VEGETARIAN FOR 21 YEARS.

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THERE can be no doubt that deficiencies in diet may play an important rôle in the development of osteomalacia. For a thorough review of the various aspects of this disease the reader is referred

to the excellent monograph by Hess (1929). The "hunger osteomalacia" among the peoples of "Central Europe" after the World War was due to gross deficiencies in diet, reminding one a good deal of the osteomalacia investigated by Maxwell and Miles (1925) and Miles and Feng (1925) in Shansi, China. The patients of these investigators had been living on a pronounced vegetarian diet, without milk or eggs, and very deficient in calcium. The ratio Ca:P was low, about 0.25 to 0.32. In her report of cases of osteomalacia in Delhi, Stapleton (1925) likewise states that the diet was vegetarian, although it contained more animal fat than the preceding. Wilson and Surie (1930) give a review of 265 cases of osteomalacia in India, and they claim that in most of these cases the diet was probably not deficient in calcium or phosphorus, but its content of vitamin D was inadequate.

Most authors are agreed that the development of osteomalacia is contingent upon at least one additional factor besides deficiencies in diet, namely, unhygienic living conditions—especially want of sunlight.

This paper gives an account of a case of pronounced osteomalacia, in which the only etiologic explanation appears to be that the patient had been a vegetarian for a number of years.

Case Record.—A. J., male, aged 55, married, post-office clerk, had always enjoyed good health. At the age of 34, he became a vegetarian, for ethical reasons, and he has kept it up since, never taking any meat or fish. His diet consisted of cereals, vegetables, fruit, potatoes and beets, and plenty of milk and eggs. The stools were always normal, neither voluminous nor fatty. At the age of 40, he had a mishap while at work: he fell and hurt his left hip. Since then, he has suffered from pains in the hip, gradually radiating down into the left thigh. These pains have been worst in the winter, and would almost subside completely in the summer; on the whole, they were steadily getting worse, and finally the patient was entirely unable to work. In June, 1931, he applied to the Medical Dispensary of the Rigs-hospital, where the diagnosis osteomalacia was made after Roentgen ray examination. The radiographs showed marked halisteresis, especially of the vertebræ and pelvis, the former appearing like fish vertebræ. The pelvis showed marked deformity with lateral contraction, most pronounced on the left side. The left hip joint was the site of very severe osteoarthritic changes, with coxa vara. The physical examination revealed no abnormalities apart from the deformities due to the bony changes.

Examination of the urine showed no pathologic elements. Wassermann and Kahn reactions in the blood were negative. The serum calcium was estimated as 10.1 mg. per cent. Unfortunately, the inorganic phosphorus content of the serum was not examined at that time.

On July 8, 1931, treatment was instituted with cod-liver oil (45 cc. daily) and calcium chlorid ($\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$, 2 gm., 3 times daily). The result of the treatment was striking. In less than 1 month the patient stated that he had improved very much, and Roentgen ray examination on October 1 showed a considerable deposition of calcium in the bones. The cod-liver treatment was discontinued, as it was disagreeable to the patient, and he was given a preparation of irradiated ergosterol (Ultranol [100 D], 30 drops daily). On October 14, 1931, the serum calcium concentration was 10 mg. per

cent; on January 13, 1932, it was 11.3 mg. per cent. He resumed work on October 12, 1931, feeling well.

The vitamin D and calcium treatment was discontinued February 27, 1932. Within a month, March 30, he complained that the old pains had begun again. At that time the serum calcium was 10 mg. per cent. The treatment was instituted anew, and the pains ceased in 3 to 4 weeks.

Experimental Study. It was planned to examine the calcium and phosphorus metabolism in this patient as far as possible under the same conditions as prior to the treatment. As discontinuance of the treatment for 1 month previously had caused a recurrence of the subjective symptoms, the treatment was now discontinued again for 1 month before the experimental studies began. The aim was to investigate: (1) The calcium and phosphorus metabolism of the patient on a diet that did not differ too much from his usual diet; (2) the effect of an addition of calcium salts to this diet; (3) the effect of an addition of phosphates. Out of regard for the time of the patient it was necessary to leave out the question of addition of vitamin D.

Treatment with Ultranol (vitamin D) and calcium chlorid was discontinued on April 30, 1932, and the patient was admitted to the Med. Dep. II, Kommunehospital (Copenhagen), on May 26, 1932.

Technique. During the experimental period the patient was allowed to be up and walk about, also in the garden of the hospital, as he was himself most painstaking in complying with the rules for collection of the urine and feces. The same diet, with a few unessential changes, was kept throughout the experimental period. Each of the 3 experiments lasted 5 days.

Diet. For the sake of simplification the diet was composed of as few food articles as possible. The calcium and phosphorus contents of these foods were estimated by average analyses (Table 1).

TABLE 1.—CALCIUM AND PHOSPHORUS CONTENTS OF FOODS IN DIET.

	Per cent Ca.	Per cent P.
Milk	0.114	0.092
Boiled potatoes	0.006	0.065
Zwieback	0.0453	0.140
Sugar	0.003	

In addition the patient was given peanut oil (not analyzed), a little vinegar (dilute acetic acid) and minimal amounts of various spices. For beverage he had weak tea and distilled water. He took this diet in a daily amount corresponding to about 2200 calories.

Feces. The feces of each experimental period were marked off by means of carmine tablets, given in the morning, 1 hour before meal, at the beginning and end of the period. When necessary, daily evacuation of the bowels was brought about by means of phenolphthalein (dose, 0.5 gm.). The stools were collected in a covered container in which the portions were mixed thoroughly by long stirring.

Urine. In each period all the portions of urine were collected and preserved by addition of a little thymol and concentrated hydrochloric acid (pure).

The analyses were carried out under the supervision of Dr. E. Gjörup, in the physiological laboratory of the Royal Veterinary College and in the laboratory of Queen Louise's Hospital for Children.

EXPERIMENT 1. In the 5 days of the experimental period (May 30 to June 3, inclusive) the patient took the diet listed in Table 2, the daily portions being equal.

In this case, then, there was a positive calcium and phosphorus balance, but certain findings in the examination of the metabolism showed that here the calcium metabolism did not follow normal lines. The absolute calcium

output in the urine was abnormally great, amounting daily to 0.3 gm. Ca as against the normal 0.09 to 0.13 gm. (Goldthwaite, Painter, Osgood and McCrudden, 1905). The urinary calcium output was also relatively large as is evident from Table 3.

TABLE 2.—CALCIUM AND PHOSPHORUS METABOLISM IN EXPERIMENT 1.

		Intake.			Output.		Retention.	
		Ca gm.	P gm.		Ca gm.	P gm.	Ca gm.	P gm.
Milk	5000 gm.	5.70	4.60	Urine	7720 gm.	1.49	4.06	
Potatoes	2700 gm.	0.16	1.75	Feces	310 gm.	2.19	1.69	
Zwieback	750 gm.	0.34	1.05					
Sugar	250 gm.	0.01						
		6.21	7.40			3.68	5.75	2.53 1.65

Retention per day: 0.51 gm. Ca and 0.33 gm. P.

TABLE 3.—CALCIUM AND PHOSPHORUS OUTPUT IN EXPERIMENT 1.

	Urine.	Feces.	Retention.
Ca in per cent	24	35	41
P in per cent	55	23	22

In calcium balance in normal individuals one-third of the calcium output is excreted with the urine and two-thirds with the feces. Here in this case, more than one-half of the calcium output was excreted with the urine. This is the more peculiar as a large part of the ingested phosphorus was demonstrated in the feces. On intake of phosphates in normal persons two-thirds of the phosphorus output is excreted with the urine and one-third with the feces. The same proportion of output is found in this case.

On May 31 the serum calcium concentration was 9.1 mg. per cent, inorganic phosphorus 3.6 mg. per cent.

EXPERIMENT 2. The effect of ingestion of calcium salts was examined in the second experimental period (June 7 to 11, inclusive).

Numerous investigations (see Peters and van Slyke) have established that the calcium and phosphorus metabolism is influenced by ingestion of acid or alkali. Acid ingestion produces an increase in the absorption of both calcium and phosphorus, whereas intake of alkali has the opposite effect. The cause of this is probably that acidity of the intestinal contents gives a production of easily soluble calcium phosphates, whereas the calcium phosphates formed in an alkaline medium are less soluble. The interaction of the various factors will then decide whether the conditions of retention are to be changed. At any rate, however, there will be a change in the distribution of Ca and P between the urine and the feces.

The calcium salts employed most commonly in therapy, calcium chlorid and calcium lactate, are both able to give an increase in serum calcium, as both salts are easily soluble. But in the organism calcium chlorid acts as an acidifying salt, while calcium lactate has the property of an alkalinizing drug.

In order to produce a strong calcium effect without altering the acid-base equilibrium, it was decided to combine the two salts: 1 gm. calcium chlorid ($\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$) was given together with 2 gm. calcium lactate (*Lactas calcicus solubilis* Merck). This combination did not cause any

change in the hydrogen ion concentration of the urine, which was determined every day in the experimental periods (Table 4).

TABLE 4.—pH OF THE URINE IN EXPERIMENTAL PERIODS.

	1st day.	2d day.	3d day.	4th day.	5th day.
Experiment 1 . . .	7.0	7.1	7.3	7.0	8.1
Experiment 2 . . .	7.1	7.1	7.1	7.1	7.2
Experiment 3 . . .	7.0	7.2	7.3	7.2	7.2

Approximately 20 gm. calcium chlorid was dissolved in 300 cc. water, and the exact calcium concentration of this solution was determined by titration with AgNO_3 . Fifteen cc. of the solution (pipette) was given 3 times daily, while calcium lactate was given in powder form (weight) 2 gm. 3 times daily.

TABLE 5.—CALCIUM AND PHOSPHORUS METABOLISM IN EXPERIMENT 2.

		Intake.				Output.		Retention.	
		Ca gm.	P gm.			Ca gm.	P gm.	Ca gm.	P gm.
Milk	5000 gm. .	5.70	4.60	Urine	7320 gm.	1.66	3.15		
Potatoes	3000 gm. .	0.18	1.95	Feces	510 gm.	4.71	1.67		
Zwieback	750 gm. .	0.34	1.05						
Sugar	250 gm. .	0.01							
Addition:									
CaCl ₂ sol.	225 cc. .	2.79							
Calc. lact.	30 gm. .	3.92							
		12.94	7.60			6.37	4.82	6.57	2.78

Retention per day: 1.31 gm. Ca and 0.55 gm. P.

Administration of calcium salts produced a marked increase in the retention of Ca and P, relatively most of Ca.

Table 6 shows that in this experiment the distribution of the Ca and P output between the urine and the feces was approximately normal.

TABLE 6.—DISTRIBUTION OF CALCIUM AND PHOSPHORUS OUTPUT IN EXPERIMENT 2.

	Urine.	Feces.	Retention.
Ca in per cent	13	36	51
P in per cent	41	22	37

At the end of the experimental period (June 12) the serum calcium concentration was 10.4 mg. per cent, inorganic phosphorus 4.7 mg. per cent.

EXPERIMENT 3. The effect of ingestion of sodium phosphate was examined in the 3rd experimental period (June 16 to 20, inclusive), by administration of a neutral solution of primary and secondary sodium phosphate, containing 0.50 gm. P per 15 cc. The secondary sodium phosphate (Natriumfosfat Soerensen) was calculated after its contents of phosphorus and dissolved in water; then the solution was neutralized with HCl. Intake of 15 cc. of this solution 3 times daily did not give any change in pH of the urine (see Table 4).

In this experiment, too, there were both a positive calcium balance and a positive phosphorus balance (Table 7). The calcium retention was only a little less than in Experiment 1, and there was a considerable increase in the calcium retention. That the phosphate addition gave a marked change

in the distribution of the Ca output between the urine and the feces is evident from Table 8.

TABLE 7.—CALCIUM AND PHOSPHORUS METABOLISM IN EXPERIMENT 3.

		Intake.			Output.		Retention.	
		Ca gm.	P gm.		Ca gm.	P gm.	Ca gm.	P gm.
Milk	5000 gm.	5.70	4.60	Urine 7520 gm.	1.13	9.86		
Potatoes	3000 gm.	0.18	1.95	Feces 580 gm.	2.95	2.63		
Zwieback	750 gm.	0.34	1.05					
Sugar	250 gm.	0.01						
Addition: Sod. phosphate sol.	225 cc.	7.50					
		6.23	15.10		4.08	12.49	2.15	2.61

Retention per day: 0.43 gm. Ca and 0.52 gm. P.

TABLE 8.—CHANGE OF DISTRIBUTION OF CALCIUM OUTPUT IN URINE AND FECES.

	Urine.	Feces.	Retention.
Ca in per cent	18	47	35
P in per cent	65	17	17

Less than one-third of the total calcium output was found in the urine. This agrees with the fact that the absolute phosphorus output with the feces increased considerably under the phosphate administration. About three-quarter of the phosphorus output was excreted with the feces, *ca.* one-quarter with the urine.

At the end of the experimental period (June 21) the serum calcium concentration was 10.5 mg. per cent, inorganic phosphorus 3.7 mg. per cent.

Comments. As already mentioned it seems natural to attribute the illness of this patient to deficiencies in his diet. But, what were the deficiencies in this vegetarian diet?

Calcium deficiency seems to be out of the question. His usual diet was very much like the diet given in these metabolism experiments that contained a good deal of calcium. Nor was his serum calcium lowered, as was the case in Maxwell and Miles' patients who had a low-calcium diet.

The same considerations apply to the phosphorus content of the diet. The metabolic diet was not low in phosphorus; and the inorganic phosphorus concentration of the serum of the patient was normal at the time of examination; but it has to be admitted that the examination was made while there was a positive phosphorus balance. Yet 1 month before the examination he was taking his usual diet without addition of vitamin D or other therapeutic agent.

There remains then the question of the vitamin D content of the diet. It may be taken for granted that the vegetarian diet, even with addition of eggs, milk and butter, may in the winter be inade-

quate with regard to vitamin D. That the illness of this patient was due to vitamin D deficiency is evidenced also by the characteristic improvement he claimed to have every summer. It is true that the effect of light suggests itself as a direct factor in this seasonal improvement, but in northern regions this factor is only of secondary importance.

Also the metabolism experiments indicate that the development of the disease in this case could not be ascribed to the calcium and phosphorus contents of the diet. In Experiment 1 the patient took a diet that corresponded very well to his usual diet. It contained plenty of calcium and phosphorus, and the ratio Ca:P was 0.8, which Toverud and Toverud (1931) consider optimal. Both the calcium balance and the phosphorus balance were positive, and yet the metabolism differed from the normal. Here was the strikingly great calcium output in the urine, a finding that is characteristic of osteomalacia (Goldthwaite, Painter, Osgood and McCrudden, 1905; Mellanby, 1932). Thus, the power of calcium absorption was not decreased, but even though phosphorus was supplied in a suitable amount, only a comparatively small portion of the absorbed calcium was deposited in the bones.

In Experiment 2 the ratio Ca:P of the diet was 1.7, and in Experiment 3 it was 0.4, that is, respectively, doubling and halving of the original ratio. Yet the phosphorus retention was increased very considerably in both experiments. It is reasonable to take these findings to mean that it was not an inadequate ratio Ca:P in Experiment 1 which here gave a smaller phosphorus retention than in Experiments 2 and 3. The significance of this ratio to the calcium and phosphorus metabolism is known in particular from experiments on rats (Schultzer, 1927).

Nor did addition of calcium or phosphorus produce any definitely significant change in the serum calcium concentration or in the inorganic phosphorus content of the serum. In this respect the case reminds one of that reported by Blumgart, Gargill and Gilligan (1929). Here the serum calcium was normal (10.3 to 11 mg. per cent), and the inorganic phosphorus level was somewhat low, but constant in spite of all treatment, also with vitamin D, at 2.1 to 2.4 mg. per cent. For the present, then, these cases of osteomalacia may be paralleled with the rickets produced experimentally in young rats by Korenchevsky (1922), as in the latter condition the rachitogenic diet was not deficient in calcium or phosphorus, but in vitamin D.

Summary. 1. A case is reported of a man, aged 55, who had been a vegetarian for the last 21 years, and who had noticed the first symptoms of osteomalacia 15 years ago. His condition improved very considerably on treatment with vitamin D and calcium chlorid.

2. The treatment was discontinued for 1 month, and then his

calcium and phosphorus metabolism was examined while on a diet that corresponded very well to his usual vegetarian diet. This diet contained optimal amounts of calcium and phosphorus. Both the phosphorus balance and the calcium balance were found to be positive. The calcium output in the urine was abnormally high.

3. The effect of intake of calcium salts was examined. There was an increase in both the positive calcium balance and the phosphorus balance.

4. Intake of phosphates also increased the positive phosphorus balance, whereas it had no particular effect on the positive calcium balance.

5. Hence one may conclude that if the osteomalacia in this case was due to deficiencies in the diet, as is most likely, it was not owing to faults in calcium and phosphorus content of the diet but to vitamin D deficiency.

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STUDIES IN PENTOSURIA.

A REPORT OF 12 CASES.

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It is unfortunate that the belief prevails that pentosuria is an exceedingly rare condition which can be diagnosed by metabolic specialists only. Because of this belief many cases are overlooked, and many more are mistreated as diabetics. It is incorrect to

assume that no harm can come of treating a pentosuric as a diabetic, particularly as the tendency is to give insulin to the latter. Administered to the pentosuric, insulin may cause hypoglycemic reactions and convulsions. In addition, when regarded as diabetic, the pentosuric is subjected to unnecessary dietary restriction.

We wish to emphasize that every glycosuria in which the concentration of reducing bodies is regularly 1 per cent or less should be regarded with suspicion and further investigated. The necessary procedures are not expensive or time-consuming and can be done in the office. The response of the patient to a meal rich in carbohydrate will often point to the correct diagnosis (see diagnosis and differential diagnosis). The fermentation test and the Bial test will yield further valuable information.

The diagnostic features of pentosuria are not well known; to illustrate this, we need only call attention to the fact that 6 of our cases were at one time or another hospitalized in various institutions without being properly diagnosed. If this paper serves only to make the reader "pentose-conscious" it will have fulfilled one of its major purposes.

Historical. In 1892 Salkowski and Jastrowitz¹ described the first case of pentosuria. In 1900 Neuberg² isolated racemic arabinose from the urine of a pentosuric. This sugar was optically inactive and formed an osazone with di-phenylhydrazin. Similar cases were described by Aron³ in 1913 and Cammidge and Howard⁴ in 1920. As a result of these studies it was assumed that inert arabinose was the only urinary pentose. In 1914 Levene and La Forge⁵ found a dextro-rotatory pentose which did not form a di-phenyl osazone and which they proved to be xyloketose. Zerner and Waltuch⁶ recovered a similar substance from the urine of their 2 cases. The pentosazone had a melting point of 162° C., and when mixed with l-xylosazone it formed a new compound (dl-xylosazone) which melted at 210° C. They believed the urinary sugar to be a member of the xylose group. Further proof of the existence of xyloketose was furnished by Greenwald⁷ who described 4 cases in 1930.

Garrod⁸ collected more than 50 cases of pentosuria from the literature in 1923, and in a recent paper Margolis⁹ reviewed 78 cases. Since then 22 additional cases have been described by the following authors: Greenwald⁷ 4 cases, Fischer and Reiner¹⁸ 4, Marble¹⁹ 3, Neuman¹⁰ 4, Leinoff¹¹ 1, Hari¹² 5, Rossen¹³ 1. These, together with our 12, total 112 reported cases.

Case Reports. CASE 1.—H. B., male, aged 6, was admitted in July, 1928, with a history of diabetes for 1 year and complaining of failure to gain weight for 2 years. Sugar had been found in his urine 1 year ago and he had been regarded as an early diabetic. Our diagnosis was pentosuria and malnutrition. The average daily excretion was 1.5 gm., calculated as glucose.

CASE 2.—J. L., male, aged 22, was admitted in February, 1932, complaining of weakness on walking, occasional double vision, and tingling sensations in the legs. In September, 1930, he had been ill due to a gastrointestinal upset. Shortly thereafter paralysis of the entire body set in. He recovered from this but soon developed urinary difficulty and weakness on walking. The neurologic diagnosis was multiple sclerosis. Sugar had been found in his urine during his stay at another hospital and he had been given as much as 60 units of insulin daily. Examination of 5 brothers failed to reveal any additional cases. The daily excretion of pentose was 3.5 gm.

CASE 3.—B. B., aged 39, was admitted in January, 1933, complaining of cough and expectoration. He had been well until September, 1931, when he began to cough and had several hemoptyses. He was sent to a convalescent home, receiving alternate pneumothorax treatments. Three months prior to admission, sugar was found in his urine and he received 15 units of insulin daily. The diagnosis was chronic pulmonary tuberculosis. The daily excretion of pentose was 3 gm.

CASE 4.—N. L., male, aged 33, was referred to us for diagnosis by a former member of the hospital house staff. He had always been well and had no complaints. In 1923 he was refused life insurance because sugar was found in his urine. Placed on a restricted diet he lost weight and was given 20 units of insulin daily in an effort to maintain his nutrition. This resulted in many hypoglycemic reactions. A diagnosis of renal diabetes was made by a medical consultant who advised him to restrict his carbohydrate intake as a precautionary measure. Recently he was granted insurance but with a higher rating. On our advice, he resumed a normal diet and has returned to his usual weight.

CASE 5.—L. B., male, aged 37, was admitted in August, 1932, with a diagnosis of coronary artery disease and diabetes mellitus. Four months previously he began to experience precordial pain, and on several occasions lost consciousness. Thirteen years ago he had been treated as a diabetic, but had never adhered to any diet. He suffers from severe headaches as do also several members of his family. Our diagnosis was psychoneurosis. The daily excretion of pentose was 4.5 gm. Seventeen other members of his family including mother, brothers and sisters and 11 of the next generation were investigated, and 3 sisters and a niece were found to have pentosuria.

CASE 6.—A. G., sister of L. B. (Case 5), aged 41, was admitted in January, 1933, complaining of headache, vomiting and pain in the right leg of 4 months' duration. While operating a sewing machine, she noticed a pain in the right leg which later spread to the hip and back. She suffers at present from pain over the heart and has severe nervous headaches. Whenever ill or upset, she vomits everything she eats. She never knew of glycosuria until our examination revealed its presence. The diagnosis was psychoneurosis and sciatic neuralgia. Daily excretion was 2.6 gm.

CASE 7.—Y. Z., sister of L. B. (Case 5), aged 29, was investigated by visits to her home. She had been confined to a hospital for treatment of backache 3 years ago, and while there, sugar had been found in her urine. Her diet was restricted and she lost considerable weight. She suffers from severe headaches and complains of nervousness.

CASE 8.—A. J., sister of L. B. (Case 5), aged 37, had never had her urine examined prior to our investigation. She has never had any serious illness but suffers from intense headaches and has migratory muscle and joint pains. She states she is very nervous and attributes this to the fact that her 2 children have spastic paralysis.

CASE 9.—S. J., female, a daughter of A. J. (Case 8), aged 10, has suffered from spastic paralysis since birth. She is unable to walk, is mentally deficient and is an inmate of a state institution. The neurologic diagnosis is

cerebral agenesis. Examination of the urine revealed the presence of pentose. This case is of interest because it represents the second recorded instance of pentosuria occurring in parent and offspring.

CASE 10.—B. L., male, aged 28, has always been well and has no complaints. In 1931 sugar was found in his urine in the course of an examination for life insurance. At Sydenham Hospital the sugar tolerance curve was found to be normal, and further investigation revealed the urinary sugar to be pentose.*

CASE 11.—M. C., female, aged 27, first consulted a physician 3 years ago because of a skin eruption. Sugar was found in her urine at this time and she was treated for diabetes, receiving as much as 90 units of insulin daily. Hypoglycemia and convulsions occurred quite frequently. She lost 10 pounds in less than a year and also became very despondent. The patient states that regardless of whether she ate or abstained from food she always had a trace of sugar in her urine. The diagnosis of pentosuria was established and at our suggestion the patient returned to her usual diet. Seventeen members of her family were examined and a brother was found to have pentosuria.

CASE 12.—J. A., male, a brother of M. C. (Case 11). Our information concerning this case is very meager, as the patient resides in a distant city and has not yet answered our inquiry concerning his medical history. At our request, he sent us a specimen of urine which was found to contain pentose. His sister informs us that he was told 2 years ago that he had diabetes.

All of the above cases are Jews.

In all cases the urine did not ferment with yeast, gave a positive test with Bial's reagent and yielded an osazone which melted at about 156° C. This osazone when mixed with l-xylosazone and recrystallized had a melting point of about 200° C. After bromination the urine still reduced alkaline copper solution but lost its reducing power upon heating with strong acid, demonstrating that a ketone rather than an aldehyde group was present. These tests in addition to polariscopic examination established the pentose as l-xyloketose.

Diagnosis and Differential Diagnosis. Were it not for the tendency to regard every glycosuria as diabetic in origin, many more cases of pentosuria would be discovered. When incorrectly regarded as diabetics, cases of pentosuria are often placed on restricted diets and are given insulin. In addition, they are refused life insurance and are often informed of the possibility that their children may inherit diabetes.

For practical purposes there are two conditions with which pentosuria may be confused—mild diabetes and renal diabetes. Based on the response to sugar tolerance tests by individuals having these diseases, it is usually possible to tell them apart quite easily. Mild diabetics are sugar-free after an overnight fast; pentosurics and renal diabetics are not. We suggest that a liberal carbohydrate meal be taken on arising and that voided specimens be examined before and after eating. If the urine passed while fasting is negative for reducing bodies and that passed 2 hours after the ingestion of

* We are indebted to the Sydenham Hospital for permission to publish this case.

the meal gives a strong reduction with alkaline copper, the condition is obviously diabetes mellitus. If both specimens contain small amounts of reducing substances, renal diabetes or pentosuria may be suspected. One expects a slightly increased spilling of sugar after a meal taken by a renal diabetic due to the temporary elevation of blood sugar, whereas the urinary excretion of sugar in a pentosuric is uninfluenced by eating. The concentration of reducing bodies in the urine in cases of pentosuria is remarkably constant, unless the individual is receiving medication (see below). The diagnosis can be confirmed by fermentation tests, by using Bial's reagent and by blood sugar studies. Preparing the osazones, one can differentiate pentosazone from glycosazone by noting the crystalline structure and determining the melting point. Later we shall call attention to a chemical property of xyloketose which makes its recognition in the urine a very simple matter.

TABLE 1.—THE URINE IN PENTOSURIA, RENAL DIABETES AND DIABETES MELLITUS.

Reducing bodies in urine:	Pentosuria.	Renal diabetes.	Diabetes mellitus.
(a) Fasting	+	+	0
(b) Two hours p. c.	+	++	+++
Fermentation of urine	Negative	Positive	Positive
Bial test	Positive	Negative	Negative
Urinary osazone:			
(a) Form	Needles	Rosettes	Rosettes
(b) Melting point	160°	204°	204°
Sugar tolerance	Normal	Normal	Diabetic

Relation to Diabetes Mellitus. Early observers reported both pentosuria and diabetes mellitus occurring in the same individual. Voit¹⁴ obtained an osazone with the melting point of a pentosazone from the urine of 12 out of 14 severe diabetics. We have examined the urine of a large number of diabetics and have failed to obtain a positive reaction with Bial's reagent. The blood sugar in our pentosuric cases was within normal limits and the tolerance for carbohydrate was unimpaired. Garrod⁸ states that the occurrence of both diseases in the same individual probably is a coincidence, due to the liability of the Jewish race both to diabetes and pentosuria. It is generally agreed that the two conditions are separate and distinct.

TABLE 2.—BODY WEIGHT AND PENTOSE EXCRETION.

Case.	Weight.	Pentose in grams (calculated as glucose).
1	37	1.5
3	127	3.0
6	130	2.6
2	132	3.5
5	173	4.5

Nature of the Urinary Pentose. Neuberg,² Aron,³ Cammidge and Howard⁴ believed the pentose in their cases to be racemic arabinose. On the other hand, Levene and La Forge,⁵ Zerner and Waltuch,⁶ Hiller,¹⁵ Greenwald⁷ and Hari¹² described the urinary sugar as

xyloketose. Our 12 cases were shown to have xyloketose in the urine. It is our belief that the latter pentose is by far the more common sugar, if indeed it is not the only one.

Relation to Body Weight. It is probable that a direct proportion exists between body weight and the 24-hour excretion of pentose.

Pentosuria, Psychoneurosis and Headache. Margolis⁹ found that 27 per cent of his collected cases suffered from headache and 77 per cent were psychoneurotic. He points out that the disease may not be completely harmless and that neurasthenia and headache may be accompaniments or complications. Four of our cases had migraine and were psychoneurotic, but they were all members of one family, and their mother, who did not have pentosuria, had migraine as well. Neuman's¹⁰ cases showed no clinical symptoms related to their metabolic disorder and all of Hari's¹² cases were perfectly normal otherwise. It is generally agreed that pentosurics have no symptoms that can be attributed to their ailment. As regards the neurasthenia, Garrod⁸ states that race and racial temperament play an important part, and the diagnosis of diabetes, commonly made, may contribute to this result.

Pentose Excretion and Drugs. Margolis⁹ observed that the excretion of pentose rose from 1.5 to 4.8 gm. following the taking of amidopyrin. He found that other drugs (codein and pantopon) also increased the urinary output of pentose. He proved that the increase in reducing bodies was due to pentose by means of quantitative osazone determinations. Amidopyrin given to patients with migraine and to normals did not produce reducing bodies in the urine. He believed that the ingestion of amidopyrin increased the output of pentose in the urine in direct proportion to the amount ingested. A possible explanation will be given later.

Reduction in the Cold.* We discovered that the urine of our patients reduced both qualitative and quantitative Benedict solution at ordinary room temperature (without heating). One cc. of urine added to 5 cc. of qualitative solution gave a positive reaction when left undisturbed for several hours. One must not confuse this with a pseudo or phosphate reaction. The phosphate precipitate is white or gray in color, whereas in cases where the test is positive, it will be found that the precipitate is golden yellow and often forms a layer or rim above the phosphate precipitate after the tube has been allowed to stand for some time.

We have used the property to reduce alkaline copper in the cold as a quick test for detecting the presence of xyloketose in the urine, especially in the presence of other reducing substances. With the exception of levulose, other sugars (glucose, maltose, lactose, xylose, arabinose and glycuronic acid) in similar weak concentration (under 1 per cent) do not reduce in the cold.

* This test has been modified; for further details the reader is referred to J. Biol. Chem., 1933, 101, 289.

By setting up tubes containing both quantitative Benedict solution and varying amounts of urine and leaving in the cold, we have also been able to determine quantitatively the amount of xyloketose present. The reading is somewhat lower than that obtained by ordinary methods. We have used this method when interfering substances were present in the urine. For example, when we fed xylose to our patient we were able to determine how much was excreted by subtracting the amount which reduced in the cold (xyloketose) from the total obtained by ordinary quantitative tests (xyloketose plus xylose).

Optical Activity. In 2 cases the urine as voided or upon concentration was dextro-rotatory, giving a specific rotation of 22° , as compared with readings of 34° and 33° obtained by Greenwald⁷ and Levene and La Forge⁵ for the pure sugar. This discrepancy may be due to levo-rotatory substances usually present in urine. In 2 other cases no rotation could be demonstrated.

Pentosazones. In each instance the osazone had the typical crystalline structure and melted between 156° and 160° , depending upon the purity of the product. When combined with the osazone from l-xylose, the melting point rose to 200° , showing that the racemic xylosazone had been formed.

We have been able to recognize this racemic xylosazone from its crystalline form without having to resort to melting point determinations. Our method is as follows: The urinary osazone is prepared in the usual manner and dried. It is then mixed with l-xylosazone in approximately equal quantities, using 95 per cent alcohol as the solvent. Several drops of this mixture are spread on a glass slide and covered with a small funnel to ensure slow evaporation. The edges of the dried film are examined under the high power of the microscope, and if the racemic compound has been formed, it will be recognized as boat-shaped crystals, totally different in morphology from the osazone formed by xylose or xyloketose.

Fig. 1 is a drawing of racemic xylosazone crystals.

Feeding of Drugs. Amidopyrin, codein and luminal administered separately caused an increase in urinary pentose. The daily ingestion of 2 gm. of amidopyrin for a period of 1 week caused a rise from a usual level of 4.5 gm. to 20 gm. Another case received 2 gm. daily for 3 days and his 24-hour excretion rose from 3 to 8.5 gm. Like Margolis⁹ we have satisfied ourselves that the increase is really due to pentose. By means of quantitative osazones, melting points and quantitative reduction in the cold we have proven beyond doubt that the reducing substance in the urine is xyloketose.

We administered potassium iodid and calcium lactate in large amounts but obtained no rise in pentose. It is well known that many drugs are excreted in the urine as compound glycuronates. These are the drugs which apparently increase the urinary pentose. Substances like potassium iodid which are excreted unchanged

and not as glucuronates, do not cause an increased pentose output. It may well be that drugs which stimulate the formation of glycuronic acid stimulate pentose formation as well. There exists an intimate relationship between l-xylose and d-glycuronic acid, since the former can be derived from the latter by splitting off carbon dioxid. Franken,¹⁶ among others, has accomplished this conversion *in vitro* and suggests that it is possible that plants derive their pentose through similar action. We are at present engaged in investigating a possible relationship between xyloketose and glycuronic acid.

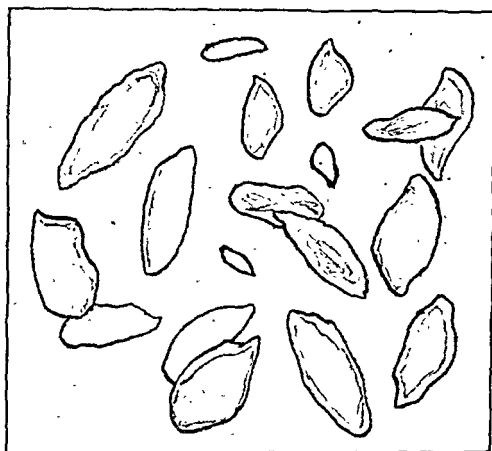


FIG. 1.—Racemic xylosazone crystals.

Metabolic Studies. The literature dealing with the feeding of various substances left us hopelessly confused and we deemed it advisable to start afresh. Urinary excretion was uninfluenced by high and low carbohydrate diets. The addition of a quart of milk (45 gm. of lactose) produced no change. Increasing the protein intake 100 gm. by feeding liver, kidney and pancreas gave negative results. These findings agree with those of Margolis.²¹ Increasing metabolism by feeding thyroid extract did not influence pentose excretion. Enforced rest in bed followed several days later by periods of muscular exercise were entirely negative. Two patients fasted for 24 hours, and as in af Klercker's¹⁷ case, their pentose excretion decreased about 50 per cent.

Feeding of Xyloketose and Xylose. We believe this to be the first instance in which xyloketose was administered to a pentosuric. Five grams of xyloketose were given by mouth, the sugar being prepared from the patient's urine according to Greenwald's method⁷ and utilized just prior to the formation of the hydrazone. The patient's excretion rose but 0.5 gm. in the next 24 hours. We attempted to rule out failure to absorb the sugar from the alimen-

tary tract by injecting 1 gm. of xyloketose subcutaneously into a rabbit and found its urine negative for reducing bodies. One of us (M. E.) also took 5 gm. of xyloketose by mouth and the 24-hour urine was completely negative for sugar. We hope to extend these experiments using the intravenous route.

Five grams of l-xylose were given to 2 of our patients by mouth and they excreted 90 per cent within the next 48 hours. A normal control acted similarly.

Greenwald²⁰ injected xylose and xyloketose into dogs and recovered 65 per cent of the former and a maximum of 15 per cent of the latter from the urine. He suggests that xyloketose may be further metabolized in the body and that it may be a product of normal intermediary metabolism. Our patient utilized or destroyed his own urinary sugar when it was fed to him. At any rate it did not appear in the urine.

Detailed results of our chemical and metabolic studies will be published elsewhere.

Summary and Conclusions. 1. Twelve cases of pentosuria are described, the sugar in all cases being l-xyloketose.

2. All cases of "glycosuria" in which the concentration of reducing bodies in the urine remains unalterably below 1 per cent should be regarded as possible pentosurics and should be further investigated.

3. By examining urinary specimens voided before and after the ingestion of a liberal carbohydrate meal, it is often possible to differentiate cases of mild diabetes mellitus, renal diabetes and pentosuria. Fermentation tests, and testing with Bial's reagent will give additional valuable information as to the nature of the urinary sugar.

4. Xyloketose reduces alkaline copper solution in the cold.

5. The crystalline structure of racemic xylosazone is described.

6. The ingestion of amidopyrin markedly increases the output of urinary pentose.

7. Pentose excretion is uninfluenced by modification of the carbohydrate or protein content of the diet. It is also unchanged by rest, exercise or thyroid extract administered by mouth.

8. When fed 5 gm. of xyloketose a pentosuric excreted but 0.5 gm. more than usual. The urine of a control taking a similar amount of xyloketose showed no reducing substances. It appears that both pentosurics and normals can utilize or destroy xyloketose when it is administered by mouth.

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EXPERIMENTAL REPRODUCTION OF LIPEMIA.

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FAT and fat-like substances are normally present in the blood plasma and corpuscles. Three principal classes of lipids are recognized: (1) common fats, which are combinations of glycerol and fatty acids; (2) phospholipids with lecithin the most common member, and (3) cholesterols. The normal concentration of these substances in the blood is somewhat variable depending upon the methods used for their determination, the state of nutrition of the individual when the blood was analyzed and upon whether the individual was or was not fasting. The following table is illustrative of the normal blood lipids and the effect of 100 cc. of olive oil on them.¹

TABLE 1.—NORMAL BLOOD LIPIDS.

Patient S.	Mg. per 100 cc.	Increase, per cent.
Fasting	439	
2 hours after 100 cc. of olive oil	467	6
4 hours after 100 cc. of olive oil	600	37
6 hours after 100 cc. of olive oil	508	13

An increase in the blood lipids may be a physiologic process following a fat meal, as shown above. If this occurs, the excess lipids disappear from the blood in the course of 12 to 14 hours. Blatherwick² has shown, in a study later confirmed by Marsh and Waller, that³ diabetic patients on diets containing fat several times in excess of that found in the normal diet, had no increase in the lipid content of the blood. If a lipemia existed when these patients first came under observation, the total blood lipids fell to normal levels on diets containing several times the normal fat content. Should the blood lipids remain high after 24 hours, some pathologic process is usually present. When the blood lipids are increased we speak of it as lipemia; when the blood plasma appears milky, as lactescence.

Pathologic lipemia may occur in a variety of conditions. In severe nephritis, pneumonia, pregnancy, obstructive jaundice, anemia, and in the xanthomata a mild increase in the lipids of the blood may be present. In severe diabetes mellitus with acidosis, a milky blood plasma is not uncommonly found. Extraordinarily high levels of the blood lipids are commonly present. In a recent collection of all cases of lipemia retinalis by Parker and Culler,⁴ 37 of the 38 reported cases were in patients with diabetes mellitus. These observers have shown in 2 reported cases of their own, which one of us (A. C. C.) studied with them, that the total lipids must be at least 3.5 per cent to produce the lipemic fundi.

Experimental lipemia has been studied by Allen in depancreatized dogs. He states that "severely diabetic dogs which digest high fat diets regularly develop some degree of abnormal lipemia, and in a minority of such animals this lipemia becomes extreme. Apart from a sufficient supply of fat in the diet, the one indispensable prerequisite for diabetic lipemia is the existence of active severe symptoms in the form of glycosuria and hyperglycemia. Mild cases with high glycosuria and severe cases with glycosuria abolished by diet never exhibit any extreme grade of lipemia, however high the fat intake. Diabetic lipemia evidently represents some secondary breakdown in fat metabolism, not directly connected with the endocrine function of the pancreas and not due merely to excess of fat in metabolism or loss of sugar from the body. There are wide variations in individual susceptibility to this disorder among both animals and patients. Tests with a wide variety of endocrine, dietary and other influences failed to reveal the nature of the disturbance or the origin of the susceptibility."

When considering the relation of acidosis to lipemia, Allen⁶ also states that "nearly every case of acidosis is attended with at least a slight lipemia, and heavy lipemia is practically never found except in connection with some degree of acidosis. This is merely a different statement of the fact that severe diabetes is practically always attended with some degree of lipemia, and that the heaviest lipemia occurs only in severe active cases on high fat diet, which naturally

gives rise to acidosis. No parallelism exists between the degree of lipemia and the degree of acidosis as measured either by the acetone of blood or urine or the CO_2 capacity of the blood plasma."

The relationship of severe diabetes mellitus to severe lipemia both in human beings and in experimentally depancreatized dogs has been shown. It appears that there is something in the diabetic state, when severe, prone to produce lipemia.

Recently we have had the opportunity to study several severe diabetics in acidosis and with lipemia. Our results in all cases were similar so only 1 case will be presented. We have attempted to determine whether there is any relationship between the lipemia and the caloric intake, ingested dietary fat, hyperglycemia and glycosuria, and acidosis. We have also studied the effect of insulin on lipemia and the relationship of the blood total lipid level to lipemia retinalis. The intake of carbohydrate, fat and protein was quantitatively controlled by weighed diets which are recorded in Table 2. The total output of acetone bodies was determined each day. Carbon dioxid combining power of the blood was done at regular intervals by the usual methods. Quantitative blood sugar determinations were done at the same time the CO_2 combining power was determined. Quantitative urinary sugar analyses were done daily. The total lipids of the whole blood were determined at regular intervals by the following method:

The blood (10 cc.) was added slowly to a mixture of 3 parts of alcohol and 1 part of ethyl ether. After standing over night the mixture was filtered and the residue washed with several portions of ether. The residue was then allowed to dry in air. It was quantitatively transferred to a 500 cc. Erlenmeyer flask, to which was then added 250 cc. of absolute alcohol. This mixture was then brought to the boiling point and maintained there for 10 minutes. The hot mixture was then filtered and the precipitate washed, first with absolute alcohol and then with ether. The combined extracts were concentrated to about 50 cc. and transferred to a separatory funnel. An equal volume of water was added and the mixture extracted several times with petroleum ether (B. P. 20° to 40°). The extracts thus obtained were made free of water by the addition of anhydrous sodium sulphate. After standing over night the Na_2SO_4 was filtered off, washed with petroleum ether, the filtrate concentrated to about 75 cc. and then made up to 100 cc. in a volumetric flask. Aliquot parts were taken from this solution and transferred to weighed flasks. The solvent was evaporated off and the lipids weighed.

Report of Case. CASE 4.—F. P., a young white male, aged 15 years, entered the University Hospital on August 6, 1931. He complained of weakness, excessive thirst, polyuria, and a skin eruption. His health had been exceptionally good until December, 1930, at which time he noticed an increase in appetite and thirst with a polyuria. He lost 30 pounds weight in 6 weeks. Weakness became pronounced and, on January 17, 1931, he passed into diabetic coma. He was then taken to a hospital where his

diabetes was well controlled, and was discharged later on a diet of 55 gm. of protein, 210 gm. of fat and 35 gm. of carbohydrate without insulin. He had no further trouble until March 15, 1931, when he discontinued weighing his food and soon developed glycosuria. Polyuria, polyphagia and polydipsia rapidly returned but less severe than formerly.

The latter part of May, 1931, he noticed white and yellowish, pinhead-sized papules on his hands, knees and elbows. They rapidly increased to pea-size with a further eruption occurring over both scapulæ, ankles and feet. For the most part they were painless, non-pruritic in nature and were typical xanthoma diabeticorum. His past history and family history are of no importance.

Physical Examination. The patient was a well developed, well nourished, well oriented and very coöperative young male. There were many pinhead- to pea-sized, hard, yellowish, xanthomatous papules over the hands, elbows, knees, ankles, forehead, buttocks and scapular regions (Fig. 1). The

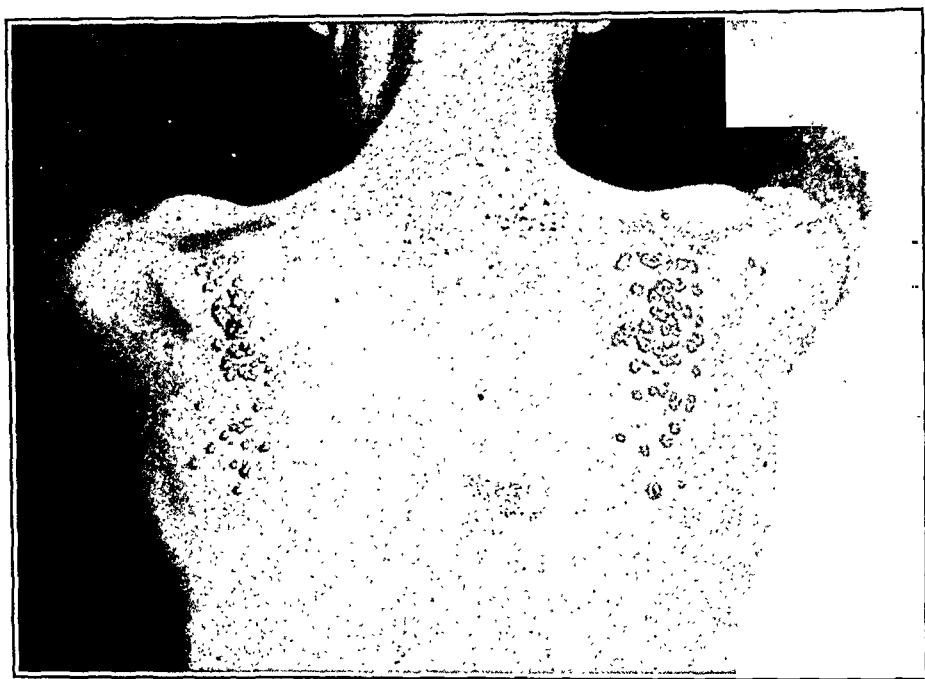


FIG. 1.—Patient No. 4, F.P. Showing the xanthoma diabeticorum eruption on the scapulæ on entrance to the hospital.

skull was symmetrical. The pupils were dilated but reacted promptly to light and in accommodation. The ocular fundi showed marked lipemia retinalis. The teeth showed lack of hygiene. The pharynx was normal in appearance. The chest was well developed; expansion was good and equal and no abnormal breath sounds or râles were present. The heart sounds were of good quality, with no murmurs. The pulse was strong and regular and the rate was 92 per minute. Blood pressure was systolic 110, diastolic 68. The results of the rest of the examination were of no interest.

Laboratory Tests. The Kahn test was negative. The urine showed a 4+ reduction in Benedict's solution. The ferric chlorid and sodium nitroprusside reactions were strongly positive. A trace of albumin and an occasional white blood cell was seen, microscopically, in the sediment. The blood examination showed hemoglobin 100 per cent (Sahli), red blood count 4,290,000 and 14,050 white blood cells. The blood smear was normal. Chest Roentgen rays were negative.

He was given a diet of 55 gm. of protein, 220 gm. of fat and 35 gm. of carbohydrate (Table 2). The available glucose of the diet was 90 gm. and the caloric value of the diet was 2340. Because of the lipemia retinalis and creamy blood serum noted when his blood Kahn was taken, a venepuncture was done on August 7, 1931, for a total blood lipid and blood sugar determination. It will be seen in Table 1 that the total blood lipids at this time were 14.170 per cent and the blood sugar 0.370 per cent. Insulin was administered in increasing doses until the patient was stabilized and sugar free on the diet. When the blood lipids were reduced to 3.020 per cent the lipemia retinalis disappeared. The output of urinary acetone bodies was high. The blood sugar fell to 0.208 per cent and the CO_2 combining power of the blood rose from 34 volumes per cent to 50 volumes per cent. The blood lipids slowly decreased to 1.780 per cent. To determine

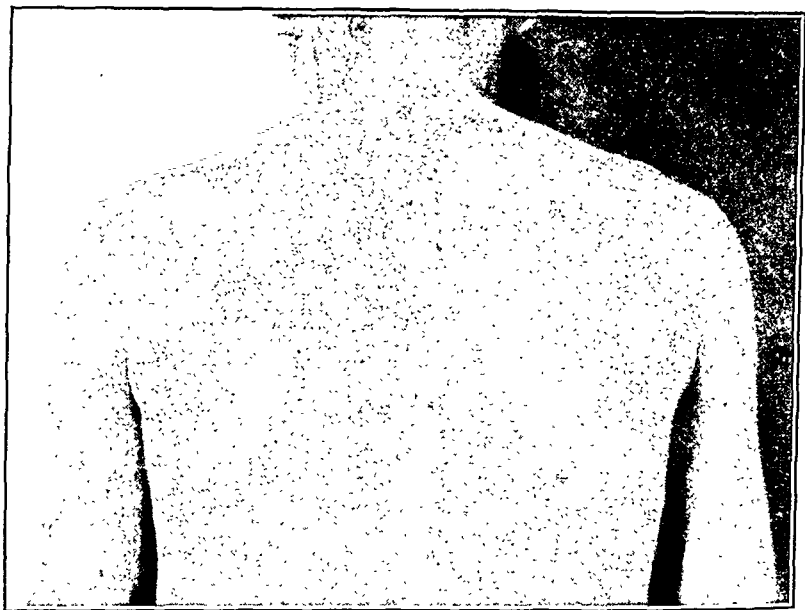


FIG. 2.—Patient No. 4, F. P. Showing the disappearance of the xanthomatous eruption with the return of the total lipids of the blood to near normal levels.

the effect of large amounts of ingested fat, a high caloric intake, and later a marked glycosuria on the lipemia, the diet was raised to 55 gm. of protein, 300 gm. of fat, and 270 gm. of carbohydrate. The calories were 4000 and the available glucose of the diet 330 gm. Insulin was given in sufficient doses to produce an aglycosuric urine and normal blood sugar. In Table 1 it will be seen that on this diet with insulin the total blood lipids fell to 1.400 per cent. The blood sugar was approximately normal, the output of urinary acetone bodies decreased and the CO_2 combining power of the blood rose to 76 volumes per cent. The insulin was then decreased in an attempt to produce a glycosuria. It had to be stopped entirely before this was accomplished. Table 1 shows that with the appearance of the glycosuria there was little change in the total blood lipids, and the xanthomata, which had been disappearing, were practically gone on September 4 (Fig. 2). When the urinary acetone bodies began to increase with a severe glycosuria, a slow rise

in the blood lipids was noted. Little effect on the CO_2 combining power of the blood was evident.

In order to produce a greater acidosis, the fat in the diet was left unchanged and the carbohydrate decreased from 270 gm. to 140 gm. This increased the F.A./G. ratio of the diet from 0.89 to 1.4. The urinary acetone bodies rapidly increased and the CO_2 combining power of the blood decreased. The blood lipids rose from 2.340 per cent to 3.480 per cent in a period of 7 days. This is an increase of 1110 mg. in 7 days compared to an increase of 250 mg. in 16 days on a diet which produced a severe glycosuria but little acidosis.

A suggestive lipemia retinalis appeared on September 25 when the total blood lipids were 3.480 per cent, but did not become characteristic until October 7 when the blood lipids were 4.350 per cent.

The carbohydrate of the diet was further reduced by 30 gm. on September 28 and again by 24 gm. on October 9, increasing the F.A./G. ratio of the diet to 1.7, then 2.0. The fat and protein of the diet were left unchanged. On these diets the CO_2 combining power fell to as low as 30 volumes per cent, the 24-hour urinary acetone body output increased to $20 \pm$ gm. and the blood lipids rose rapidly to 6.41 per cent. Because the patient was quite acidotic at this time, insulin was again administered without any change in the diet. The CO_2 combining power of the blood rose to 49 volumes per cent, the urinary acetone bodies decreased from 19.960 gm. per 24 hours to 0.711 gm. per 24 hours and the total blood lipids fell from 6.410 per cent to 1.080 per cent. Following a period of 4 days on the original high fat, high carbohydrate, and high caloric diet, the patient was then given a diet of 60 gm. of protein, 280 gm. of fat and 65 gm. of carbohydrate with insulin. This diet has a F.A./G. ratio of 2.2. Even though the fat and the ratio of fatty acids to the glucose in this diet are comparatively high, the total blood lipids fell from 0.952 per cent to 0.664 per cent, which is normal.

Discussion. There are many similarities in the results of this study and Allen's findings in lipemia of experimentally depancrea-tized dogs.⁷ It substantiates his studies that in order to have a severe lipemia the diabetes must be severe. It also confirms his findings that severe diabetes, abolished by diet or insulin, does not exhibit any extreme grade of lipemia. We do not believe, however, that there is a lack of parallelism "between the degree of lipemia and the degree of acidosis as measured either by the acetone of the blood or urine or CO_2 capacity of the blood plasma" for we have shown such a relationship to exist. This study also agrees with Allen's experiments, which show that though lipemia is attended by intense glycosuria and hyperglycemia there is a lack of parallelism between them, inasmuch as the disturbances of sugar metabolism may occur without the lipemia. We have shown that ingested fat is unimportant in the reproduction of lipemia as long as it is combusted or stored. Glycosuria and hyperglycemia have little effect on lipemia until the combustion of carbohydrate is so diminished that fat combustion becomes incomplete and acidosis occurs.

It is our belief that the lipemia of diabetes mellitus is a result of an almost total diabetes due either to the disease itself or to an accompanying severe acidosis, making less efficient what little endogenous insulin may be present. In this case there was little carbo-

hydrate oxidized and, as a result, the fat released from the storehouses or absorbed from the alimentary tract accumulated in the blood and reproduced a lipemia. We have shown that the administration of insulin to a patient with a lipemia, experimentally reproduced by diet, caused either a combustion or deposition of the excess blood fat even though the dietary fat was large in amount.

Though there was a slight increase in the blood fat during the period of glycosuria there also was a progressive increase in the urinary acetone bodies. The lipemia seems to be in proportion to the acidosis throughout the entire study, disappearing with a return of the acid base equilibrium to normal and reappearing with the event of acidosis. The lipemia retinalis disappeared when the total blood lipids were 3.020 per cent and began to reappear when the total blood lipids were 3.480 per cent. It did not become a frank lipemia retinalis until the total blood lipids were 4.350 per cent. It was necessary for the blood lipids to be higher in this case, to produce a lipemia retinalis, than in the 2 cases reported by Parker and Culler.

There seemed to be a relationship between the xanthomata and the lipemia, inasmuch as these tumors disappeared when the blood fat was reduced to near normal levels. This observation has been noted before.⁸ They did not reappear, however, when the lipemia was experimentally reproduced. This may have been due to the short time the experimental lipemia was maintained.

Conclusions. 1. A severe diabetic in acidosis with lipemia, lipemia retinalis and xanthomata was studied and a marked lipemia and lipemia retinalis were reproduced.

2. On a high fat, high carbohydrate, and high caloric diet the lipemia did not reappear when sufficient insulin was given to control the diabetes. Little rise in the total blood lipids was noted with a severe glycosuria and hyperglycemia. By removing carbohydrate from this diet and thereby increasing the F.A./G. ratio from 0.89 to 2.0, an increasing acidosis was produced as measured by total acetone body excretion and CO₂ combining power determinations. With the increase in acidosis there was a corresponding increase in the total blood lipids which reached 6.410 per cent. The administration of insulin to the patient on this latter diet caused the blood lipids to fall to 1.080 per cent.

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A CASE OF HYPERPYREXIA (110.5°) IN ARTIFICIAL FEVER THERAPY.

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THE treatment of general paresis by means of artificial fever therapy has been much used in the last decade and it is reasonable to suppose that sometimes very high temperatures have been produced. Although the literature contains many references to high fevers observed in definite pathologic conditions, I have been unable to discover any case of hyperpyrexia of 110° as the result of artificially produced fever. This report is therefore of unusual interest.

Holt¹ reported a case in which the patient's temperature reached 114°. The patient had an ear infection, and following recession of the temperature, fully recovered with no ill effects from the high temperature.

Gauss and Meyer² discussed a series of 158 patients admitted to the Cook County Hospital suffering from heat stroke. Of the number of patients admitted, 63 died of whom 46 had temperatures of 105° or over on admission. They also reported a series of 38 patients suffering from influenza, all of whom had temperatures of 110°, and all of whom recovered.

Johnson³ mentioned a case of heat stroke in which the temperature was 110° and the patient recovered.

Pierce⁴ reported a case of uremia in which the patient's temperature reached 110°, and remained at that level for 5 weeks. At the time of the publication the patient was doing well.

Brown⁵ cited a case of measles with recovery after the temperature had reached 110°.

Behneman⁶ added another report in which recovery followed after the patient's temperature had reached 110°. The patient was suffering from measles.

In the case reported a temperature of 110.5° was reached, and the recovery from the hyperpyrexia was without sequence.

Case Report.—The patient was admitted to this hospital on November 26, 1932. He then weighed 132 pounds, and was 5 feet 9 inches tall. His *physical examination* disclosed no pathologic findings other than pupils that reacted sluggishly to light changes, but well in accommodation. The blood Wassermann and Kahn were 4+. The spinal fluid Wassermann was also 4+, with a negative Pandy reaction and 11 cells present. The Lange gold curve was 45322111000. He was classified as a case of general paresis, cerebral type.

On December 19, 1932, this patient was given his first artificial fever therapy by means of our specially devised electric cabinet. The highest temperature desired and reached was 106° and the treatment was considered satisfactory.

On December 23, 1932, he was given another treatment which was started at 8 A.M. At that time the temperature of the patient was 98.4°, the pulse 96, and the respirations 20. At 9 the axillary temperature was 100.6, pulse 100, and respirations 24. The patient was perspiring profusely. At 10 the axillary temperature was 104.4°, pulse 108, and respirations 24. The number of lights in the cabinet was reduced by one-half. Fifteen minutes later the axillary temperature was 104.8; this was checked by a rectal temperature which was the same. The lights were turned off now. At 10.30 o'clock the rectal temperature was 106.2, pulse 136, and respirations 26. The patient was perspiring profusely at this time, and according to our rules of treatment was removed from the cabinet and placed in bed. He soon became restless and combative, and was handled with much difficulty. The temperature continued to rise in spite of ice cold baths and sponges and by 12 o'clock was 110.5°; the pulse was not obtainable; respirations over 60 per minute; the patient was cyanotic and comatose. From this time on the temperature dropped rather rapidly and at 1 o'clock the rectal temperature was 102.8° and thereafter came down as usual and was normal at 7.00 P.M. The pulse was not obtained until 3.15 P.M. when it was 120, and the respirations were then 32 per minute, though progressing favorably with the temperature.

At the height of the temperature the patient was given strychnin and adrenalin intravenously in small doses every 3 minutes. Artificial respiration was necessary from 12 to 12.30 P.M.

During the next 4 days the patient was apathetic and listless, but gradually grew stronger, and at the end of 4 days appeared to have reached the state normal to time prior to this treatment, in fact was alert mentally, and was more coöperative than before the high temperature.

A spinal fluid examination 2 weeks afterward gave a 4+ Wassermann reaction, negative Pandy, and 19 cells per c.mm.

Since this episode he has been given several similar heat treatments, and in no case has the temperature risen beyond our regulative temperature of 106.2°. We have no explanation to offer for the extreme rise.

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AMYLOIDOSIS AND AMYLOID NEPHROSIS.

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It is unfortunate that one must begin a clinical and pathologic study of amyloidosis without basic knowledge of either the composition or the formation of amyloid. The time honored formula of

Krakow, in 1897, making amyloid a combination of protein and chondroitin-sulphuric acid has been repeatedly questioned. Hanssen, in 1908, was unable to confirm it. Mayeda, in 1909, found no evidence of sulphuric acid in amyloid. Eppinger, in 1921, isolated a tumor mass of amyloid and found that it contained no sulphur at all. While the experimental production of amyloidosis is very interesting it has not as yet thrown any definite light on the formation of amyloid in human beings. Relatively few observations have been made on the clinical characteristics of amyloid disease because the condition is encountered in the average general hospital only on rare occasions. At the Montefiore Hospital, however, the type of case admitted made it possible to study a fairly large series.

The survey comprised a 6-year period, between the years of 1927 and 1932, inclusive. During this time there were 1727 necropsies performed on all types of cases, among which were found 125 cases of amyloidosis (7.2 per cent). The cases of amyloidosis were found in the following diseases:

TABLE 1.—DISEASES REVEALING AMYLOIDOSIS.

	No. of cases.		No. of cases.
Tuberculosis	110	Chronic lymphatic leukemia	1
Carcinoma of lung	4	Lues	1
Pyonephrosis	4	Chronic arthritis	1
Carcinoma of stomach	1	No known preëxisting disease	1
Carcinoma of esophagus	1		
Multiple myeloma	1	Total	125

Of the total 1727 cases, there were 1276 non-tuberculosis cases and 451 tuberculosis cases. This made the incidence of amyloidosis in the non-tuberculosis group 1.2 per cent, and in the tuberculosis group 24.4 per cent. The incidence of amyloidosis in patients with fatal pulmonary tuberculosis was found by Fishberg to be practically the same in a larger series. The importance of tuberculosis in amyloid disease was stressed by Saleeby, who reported it to be the etiologic agent in 41 out of 50 cases of renal amyloidosis. Of the other 9 cases in his series, 6 were due to neoplasm and 3 he ascribed to chronic nephritis.

TABLE 2.—THE DISTRIBUTION OF AMYLOID AMONG THE VARIOUS ORGANS.

	Tuberculosis group (110 cases).		Non-tuberculosis group (15 cases).	
	No. of instances.	Per cent.	No. of instances.	Per cent.
Spleen	98	89.1	10	66.7
Kidney	79	71.8	8	53.3
Liver	69	62.7	7	46.7
Adrenal	45	40.9	5	33.3
Lymph node	9	8.2	0	0
Parathyroid	5	4.5	0	0
Pancreas	3	2.7	0	0
Intestine	2	1.8	0	0
Stomach	1	0.9	0	0
Heart	1	0.9	1	6.7
Rectum	1	0.9	0	0
Tongue	1	0.9	1	6.7
Myelomatous tissue	0	0	1	6.7

Despite the disproportion of the total number of cases in the two groups of Table 2, the similarity of distribution of the amyloid throughout the organs suggests a parallel mechanism of deposition regardless of the underlying disease. Of the four organs of major importance in amyloidosis, namely, spleen, kidney, liver and adrenal, only the spleen and kidney were ever involved alone—the spleen 12 times and the kidney twice. The frequent association of bone and lung disease with amyloidosis has been attributed to the chondroitin content of these organs. Table 1 shows that 117 (93.6 per cent) of the cases were of this type.

The large number of cases in the tuberculosis group, coupled with the unity of the basic disease, made this group very suitable for a study of the clinical and pathologic aspects of amyloidosis. Of the 451 tuberculosis patients, there were 54 instances of suppurative lesions such as purulent pleural effusions or draining bone sinuses. This latter division contained 19 cases of amyloidosis (35.2 per cent), as contrasted with 24.4 per cent for the general incidence of amyloidosis in all the tuberculosis cases. The 110 tuberculosis amyloid cases included 106 of pulmonary tuberculosis and 4 of bone tuberculosis. The pulmonary tuberculous lesions were divided into 74 dominantly fibrocaseous, and 32 dominantly fibroid. The osseous tuberculosis cases consisted of 3 hip disease and 1 Pott's disease. The age of the patients ranged between 16 and 68 years, with the greatest number of cases, 29, falling in the age group between 30 and 40 years. This was followed by a gradual decline in the succeeding decades. There were but 5 cases below the age of 20, but this could be partly explained by the small number of admissions to the hospital of that age group. The clinical duration of the tuberculous process in these patients ranged from 6 months to 40 years, with 19 patients giving a history of less than 2 years and 59 of less than 5 years.

In regard to complications there were 74 patients with tuberculous complications, 9 with non-tuberculous complications, and 27 with no complications. The most common complication was enteric tuberculosis, which occurred 46 times. The other common tuberculous complications were laryngeal, genito-urinary, and meningeal involvement. The most common non-tuberculous complication was diabetes mellitus, which occurred 9 times. The variety and incidence of the complications did not differ from those generally found in all tuberculosis cases.

Examination of the urine of 109 of the amyloid cases revealed albuminuria in 77. Among these were found 65 with amyloid involvement of the kidney and 12 without such involvement. Further analysis of the latter group showed that in 8 of the 12 cases the albuminuria could be readily accounted for by such conditions as nephrolithiasis, renal abscess, nephrosclerosis, genito-urinary tuberculosis, etc., leaving 4 cases in which the albuminuria was

due to neither renal amyloidosis nor other apparent cause. In the 79 cases of renal amyloidosis (Table 2) the incidence of albuminuria was 82.3 per cent. It is seen, therefore, that albuminuria occurring in a case of amyloidosis is usually indicative of renal involvement. It is necessary, however, first to exclude local causes. The converse is not necessarily true, for there were 14 instances in which renal amyloidosis occurred without albuminuria. There were 3 negative cases with urine examination within 2 weeks of death, and 1 on the day preceding death. Saleeby, investigating this problem, found albuminuria to be present in 29 out of 40 cases of renal amyloidosis.

Hypotension is a common occurrence in patients with chronic pulmonary tuberculosis. The amyloid cases were investigated to determine if amyloid involvement of the kidneys could produce an elevation of the blood pressure in this type of patient. In the entire series of renal amyloid cases there was found no systolic blood pressure which exceeded 140 mm., and there were only 4 cases which exceeded 130. These figures are similar to those observed among all patients with progressive pulmonary tuberculosis. In cases of amyloidosis in which the underlying disease is not as chronic as pulmonary tuberculosis, amyloid involvement of the kidney has occasionally been found associated with hypertension and also retinal changes. In this series there were no retinal changes observed.

Of the organs which are usually affected in amyloidosis, the kidney appears to be the only one, involvement of which may lead to death. Renal insufficiency as a terminal phenomenon in renal amyloidosis plays an important part in the prognosis. While amyloid involvement of the liver, spleen, or adrenals may be very extensive, there is apparently no direct evidence that death ever resulted from these complications. It would appear, therefore, that if the patient with amyloidosis did not go into uremia, the prognosis, while grave because of the existence of amyloid degeneration, depended actually on the course of the underlying disease. The problem of renal insufficiency in amyloidosis is being investigated at the present time by Dr. Leonard Tarr and will be reported subsequently.

There is one phase of renal amyloidosis, namely, amyloid nephrosis, which is of great interest, particularly from the standpoint of pathogenesis. The kidney of amyloid nephrosis is generally described as being increased in size with a capsule that strips easily. Upon section, grossly, there presents a yellowish surface and usually some widening of the cortex. The reaction with Lugol's stain is strongly positive, bringing the glomeruli into prominence. Microscopically, the amyloid is confined almost entirely to the glomerular tufts where the involvement varies from partial replacement to complete obliteration. There is only slight amyloid deposition along the basement membranes of the tubules. The most prom-

inent changes in the tubules are those of fatty degeneration associated with hyalin and droplet degeneration. In addition, the tubules are swollen and the lumina are dilated and filled with casts. In the later stages there is seen marked tubular atrophy. Doubly refractile fat is found in the interstitial tissue. The clinical syndrome associated with this pathologic condition is that of nephrotic edema. In discussing the pathogenesis of this complex the nephrotic feature is the one which has usually been emphasized. Epstein, in considering the importance of extrarenal factors in nephrosis, accepted the tubular degeneration as a result of the metabolic disturbance, with the amyloid changes as either independent or incidental. Fahr also considered the amyloid kidney as a form of nephrosis due to toxic causes. The dual character of the disease has also been stressed with the contention that in amyloid nephrosis there are two associated conditions present in the kidney—amyloidosis and lipoid nephrosis. Fahr reported an associated lipoid nephrosis in 16 out of 19 cases of amyloidosis with edema. Shapiro stated that while amyloidosis and lipoid nephrosis occur simultaneously, both are independent as to origin and histology, and that either may become far advanced without the other. He further added that while lipoid nephrosis is relatively benign, amyloidosis is grave and hopeless, and that the former may completely obscure, clinically, even advanced amyloidosis. Similar observations were made by von Nogens. More recently Fahr has inclined to the view that the tubular changes do not represent primary disease but are secondary to glomerular damage.

Investigation of the 79 cases of renal amyloidosis along these lines revealed 27 cases (34.1 per cent) in which the kidneys were typical of amyloid nephrosis and in which, in addition, were presented the clinical features of edema and marked albuminuria. Seven of these cases had low total serum proteins with inversion of the serum albumin : serum globulin ratio as corroborative evidence of the nephrotic character of the edema. The remaining 20 cases had no serum protein determinations but presented no features which suggested that the edema was other than nephrotic. In all of these 27 cases the microscopic sections of the kidneys were similar and uniformly presented the features of amyloid obliteration of the glomeruli, and dilatation and degeneration of the tubules.

It was noted, however, that sections of the cases which had had no edema and little albuminuria also bore some resemblance to the kidney of amyloid nephrosis, and that in many instances the similarity was marked to a very high degree. Both types of cases had amyloid infiltration of the glomeruli and degeneration of the tubules. The main difference appeared to be one with respect to the degree of involvement only. In the cases with edema and

marked albuminuria there was extensive amyloidosis with obliteration of the glomeruli and marked degenerative tubular change; whereas, in the cases without edema there was less glomerular destruction and less tubular degeneration. In going over the series with Dr. David Perla, of the pathology department, there were no instances noted in which extensive amyloidosis of the glomeruli was associated with minimal tubular change, or in which severe tubular degeneration was associated with minimal deposition of amyloid in the glomeruli. This implied an intimate relationship between amyloidosis and the lipid nephrotic changes. If the cases which showed lipid nephrosis were only those with extensive amyloidosis, a complete dissociation of the two diseases seems unlikely, particularly in view of the observations that gradations in the extent of the amyloidosis were associated with gradations in tubular degeneration. In dividing the amyloid kidney into four stages, Fahr made these gradations the basis of his classification. It strongly suggested, therefore, that the differences between the simple amyloid kidney and the amyloid kidney with lipid nephrosis are quantitative ones—one stage leading to the other with progression of the amyloidosis. The basic cause of the nephrotic syndrome is, then, not a separate lipid disease but rather a severe amyloidosis. The greater the destruction of the glomeruli, the more severe is the albuminuria. With the loss of protein in the urine there is produced a general lowering of the serum albumin and the total protein. When the serum proteins have been sufficiently lowered, the resulting diminished osmotic pressure of the blood is responsible for the production of edema in the same manner that has been described for its production in chronic lipid nephrosis, by Epstein. The problem in amyloid nephrosis is therefore one of glomerular disease with the tubular changes secondary to, or intimately related with, the glomerular damage. When a patient with amyloidosis develops the nephrotic syndrome it is indicative of extensive amyloidosis of the kidneys.

In the experimental production of amyloidosis in rabbits by subcutaneous injections of manganese chlorid, Butt found that in addition to extensive infiltration and obliteration of the glomeruli by the amyloid there was also produced fatty degeneration, swelling and dilatation of the tubules. He also observed that the albuminuria was greatest where the amyloidosis was most severe. Jaffé produced amyloid disease experimentally with repeated injections of nutrose and found that, after many injections, the kidney resembled that of amyloid nephrosis very closely.

It is difficult to explain the lipoidal character of the tubular degeneration. If a general lipemia had been demonstrated, a relationship with the fatty changes in the kidney might have been suggested. In lipid nephrosis, Epstein believes that the kidney

participates in the general metabolic changes due to increase of lipoids in the blood. The experimental production of hypercholesterinemia in rabbits by Dewey resulted in fatty infiltrative changes in the kidney, associated with tubular degeneration in practically all instances. The infiltrations, however, were of a localized type. There is considerable experimental evidence by the Fishbergs and Leiter that the presence of low blood proteins can be responsible for a rise in blood fats. The explanation offered is that the increase in fats is a compensatory mechanism to raise the osmotic pressure of the blood. In this series, unfortunately, there were no determinations of the total blood fats and too few of cholesterol to be of any significance.

The Congo red test is now used extensively on the tuberculosis wards as one of the diagnostic criteria in amyloidosis. In this series, however, only 9 cases had the test performed. The results ranged from 60 to 100 per cent retention of the dye in 1 hour. All of these cases showed extensive amyloidosis of the organs affected. It is interesting to note that 1 of the cases with 95 per cent retention had only the kidneys and adrenals involved, in view of the importance which has been placed on the liver as being largely responsible for retention of the dye by Bennhold, Bookman and Rosenthal, and others. In the non-tuberculosis group there was an 85 per cent retention in a case of multiple myeloma in which the amyloid was deposited only in the myelomatous tissue. As far as interpretation of the test is concerned, the results of a large series of examinations done by Dr. Samuel Melamed, of the hematology department, have led us to make positive diagnoses of amyloidosis only where retention of the dye has exceeded 50 per cent. Retention of between 25 and 50 per cent is considered doubtful. Less than 25 per cent is regarded as negative. These figures conform, with minor variations, with those generally accepted.

A clinical study of the patients on the tuberculosis wards was also made. There were 15 cases which, because of hepatomegaly, albuminuria and positive Congo red test, warranted the diagnosis of amyloidosis. Five of these cases were edematous. The albuminuria in the edematous cases ranged between 4 and 8 gm. daily; the albuminuria in the non-edematous cases ranged between a trace and 7 gm. daily. The relation between albuminuria and serum proteins is listed below.

It is noted that although the albuminuria in some of the non-edematous cases was as great as that in the edematous cases, the total protein level of the former was higher. This confirms that it is the lowered serum proteins which are immediately responsible for the production of edema and that there is no direct relation between the extent of the albuminuria and the production of edema. In 3 cases the edema developed under observation.

TABLE 3.—RELATION BETWEEN ALBUMINURIA AND SERUM PROTEINS IN THE EDEMATOUS AND NON-EDEMATOUS PATIENTS.

(A) Cases With Edema.					
Patient.	Albumin- uria (gm. daily).	Serum albumin	Serum globulin	Total protein	Albumin- globulin ratio.
		(gm. per 100 cc. blood).			
I. S.	4	2.83	2.06	4.89	1.4
A. K.	8	1.96	2.36	4.32	0.8
S. T.	4	2.11	2.10	4.21	1.0
L. K.	5	1.55	3.77	5.32	0.4
H. W.	6	1.78	2.25	4.03	0.8
Average: 5.4		Average: 4.55			

(B) Cases Without Edema.					
Patient.	Albumin- uria (gm. daily).	Serum albumin	Serum globulin	Total protein.	Albumin- globulin ratio.
		(gm. per 100 cc. blood).			
S. Z.	7	3.21	3.73	6.94	0.9
N. T.	0.25	4.05	3.33	7.38	1.2
B. S.	0.25	2.98	3.90	6.88	0.8
A. G.	5	2.98	2.74	5.72	1.1
R. G.	0.5	3.05	4.99	8.04	0.6
J. K.	4	4.13	2.53	6.66	1.6
J. G.	5	4.23	2.47	6.70	1.7
E. K.	Trace	3.59	1.99	5.58	1.8
R. H.	2	2.53	2.25	4.78	1.1
H. L.	5	4.28	3.38	7.66	1.3
Average: 2.9		Average: 6.63			

CASE 1 (S. T.).—The urine was negative on admission. Two months later a trace of albumin was noted. Four months later the albumin was recorded as 2+. The albuminuria increased and 7 months after admission the patient was spilling 7 gm. per liter. At this time edema was noted and a blood chemistry examination showed low serum proteins with reversal of the serum albumin: serum globulin ratio.

CASE 2 (I. S.).—On admission had albuminuria of 3+ and total protein of 5.72 gm. per cent, with serum albumin of 3.55 and serum globulin of 2.17. One month later edema developed. At this time he had albuminuria of 4+ (8 gm. per liter) and total protein of 4.89, with serum albumin of 2.83 and serum globulin of 2.05, the loss of protein being mainly that of serum albumin.

CASE 3 (A. K.).—On admission the urine was negative. One month later a trace of albumin was noted. The albuminuria increased, and 3 months after admission was 3+. The total protein level was at 5.32, with serum albumin of 2.96 and globulin of 2.36. The Congo red test showed 54 per cent retention. Six and a half months after admission edema was noted. At this time the albuminuria was 8 gm. per liter and the total proteins had fallen to 4.32. This lowering of protein was entirely due to loss of serum albumin, which was reduced to 1.96. The Congo red test then showed 90 per cent retention.

The progressive retention of the dye in Case A. K. from 54 to 90 per cent associated with the increasing albuminuria and the development of edema demonstrates that the progress of the amyloidosis paralleled the production of the nephrotic syndrome. This is the same conclusion that was arrived at from the pathologic study.

The point was again demonstrated in the case of S. Z. who had no albuminuria on admission, but $2\frac{1}{2}$ years later was spilling 2+. At this time the Congo red test showed 10 per cent. Three months later the albuminuria was still 2+ and there was 35 per cent retention. After 3 more months the albuminuria was 3+ (2.5 gm. per liter) and there was 70 per cent retention of the dye.

Although the prognosis is obviously poor when the nephrotic syndrome complicates amyloidosis, if uremia does not supervene, it seems that death probably results from the underlying disease just as in the other cases of amyloidosis. Cases S. T. and L. K. each lived more than 4 months after the development of the nephrotic syndrome and died as a result of progression of the pulmonary tuberculosis. Case I. S. lived only a month after development of edema, but his death was due to a spontaneous pneumothorax. Case A. K. is still alive more than 4 months after showing edema. In general, the edema has rarely been extensive and the patients have usually been unaware of its existence until examination.

The urinary findings in the clinical study were of no significant diagnostic value outside of the albuminuria. Concentration was generally unimpaired. Numerous hyalin and granular casts and occasionally waxy casts were found, particularly in the nephrotic patients. White blood cells and red blood cells showed their occasional appearance. Repeated polariscopic examinations of the urine of the nephrotic patients were rarely successful in the discovery of doubly refractile bodies. A summary of the blood findings in the 15 cases revealed a lowering of the serum proteins associated with albuminuria, and an absence of nitrogen retention in all but 1 case (H. W.), who was also clinically in uremia. Calcium and phosphorus determinations in 6 of the cases revealed no significant changes. Three of the 5 nephrotic cases showed hypercholesterinemia, as did also 1 of the non-nephrotic cases.

It is felt, in conclusion, that the term, amyloid nephrosis, is a misnomer if it is used to designate a distinct pathologic entity. It is merely a form of renal amyloidosis in which the process has shown marked progression. There is justification of the use of the term, clinically, to describe the syndrome of nephrotic edema associated with amyloidosis of the kidneys. The diagnosis is readily established on the findings of edema, albuminuria, absence of hypertension, low serum proteins with reversal of the albumin: globulin ratio, and a positive Congo red test. In patients with chronic pulmonary tuberculosis the diagnosis can be made with relative certainty even before confirmation with the Congo red test. Of secondary importance in diagnosis, from a practical viewpoint, is the presence of hepatomegaly, waxy casts, doubly refractile bodies, and elevated cholesterol.

Summary. 1. A study of 1727 necropsies in a general hospital for chronic diseases revealed the occurrence of amyloidosis in 7.2 per cent of the cases.

2. The incidence of amyloidosis in the tuberculosis patients was 24.4 per cent as compared with 1.2 in the non-tuberculous. In the tuberculosis patients with suppurative lesions the incidence was 35.2 per cent.

3. The organs which showed the most frequent deposition of amyloid were spleen, kidney, liver and adrenal, in the order named.

4. A clinical survey of 110 tuberculous amyloid patients revealed that the greatest number of cases occurred in the fourth decade, that most of the cases had dominantly ulcerative pulmonary tuberculosis, and that almost one-fifth of the cases were ill less than 2 years.

5. Albuminuria was noted in 77 instances (70 per cent) of the cases. In 65 of these (84.5 per cent) it was associated with renal amyloidosis. There were 14 instances, out of a total of 79, in which renal amyloidosis occurred without albuminuria.

6. There was no instance of hypertension in any of the tuberculosis cases with renal amyloidosis.

7. Amyloid nephrosis occurred in 34.1 per cent of the cases of renal amyloidosis.

8. Pathologic and clinical studies indicate that the kidney of amyloid nephrosis is merely a type of advanced renal amyloidosis. It is unnecessary to assume the existence of a separate lipid disease associated with the amyloidosis.

9. The diagnosis of amyloid nephrosis may be made, with relative certainty, in the presence of the nephrotic symptom-complex and a positive Congo red test.

10. Unless renal insufficiency supervenes, the prognosis in amyloidosis is usually dependent on the course of the underlying disease.

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ASSOCIATION OF PITUITARY TUMOR AND PEPTIC ULCER.

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CUSHING¹ has recently called attention to the relationship between lesions of the interbrain and peptic ulcer. He reported the death of 3 patients from acute perforation in the upper alimentary tract soon after operations on cerebellar tumors. During the past year the opportunity has arisen to study 2 patients with pituitary tumors in each of whom there was found, in addition, a peptic ulcer. Careful review of the literature failed to reveal a single reported case in which a diagnosis of pituitary tumor associated with peptic ulcer was made during life.

Inasmuch as Cushing² has expressed the opinion that all known primary pituitary disorders caused marked secondary changes in the adrenal cortex, and since McLaughlin³ has recently been able to produce intestinal ulceration repeatedly after damage to the suprarenal of the dog, it was felt that the 2 cases reported below might supply a missing link in the chain of evidence connecting some cases of peptic ulcer with a basis of endocrine or sympathetic nervous system imbalance.

Cushing stated that experimental lesions anywhere in the intracranial course of the cranial autonomic stations of the midbrain or medulla (from the anterior hypothalamus to the vagal center) are prone to cause gastric erosions, perforations, or ulcers, presumably from a lack of balance between the sympathetic and parasympathetic nervous systems. Intracranial injuries and diseases affecting these same basilar regions of the brain are known to be accompanied by ulcerative lesions of the upper alimentary canal. He has also shown that stimulation of the postulated parasympathetic center by intraventricular injections of pilocarpin or pituitrin cause, in man, an increase in gastric motility, hypertonus, and hypersecretion, leading to retching and vomiting.

Case Reports. CASE 1. (No. 32-9771.)—The patient, a white girl, aged 19 years, was admitted to the Medical Clinic of Dr. Alfred Stengel in the University Hospital, March 16, 1932. Except for amenorrhea, she was perfectly well until the latter part of October, 1931, at which time she became constipated, having about 1 bowel movement per week. Various laxatives were without effect and relief was afforded only by enemas. Stools had always been normal in appearance except on one instance, November, 1931, when a hard tarry movement was seen following an enema.

One week following the onset of constipation, the patient began to vomit very irregularly—about once or twice a day. There were periods of complete freedom from vomiting, lasting for several days, the vomiting occurring

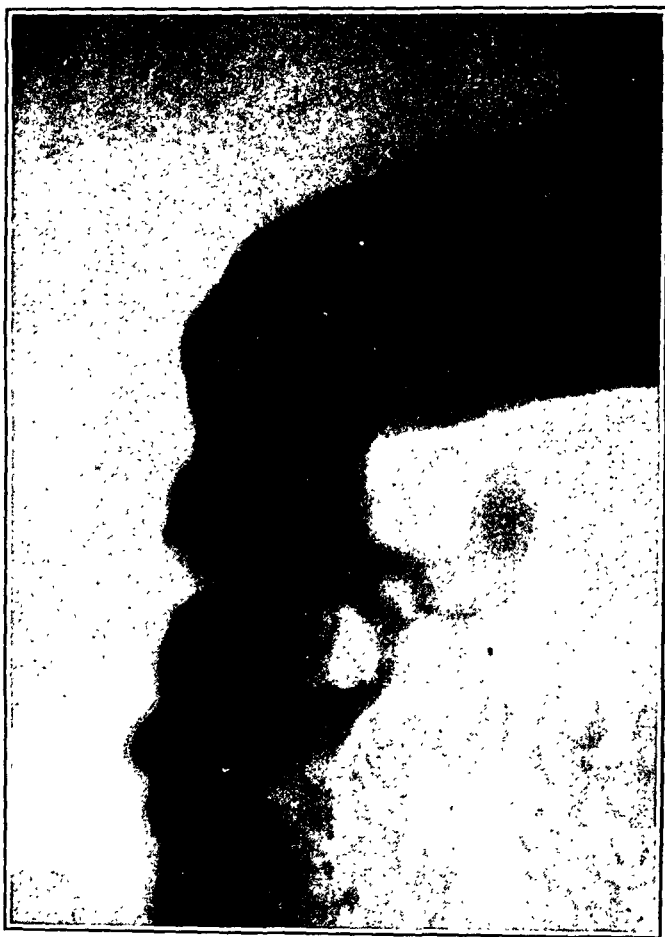


FIG. 1.—Penetrating ulcer in second portion of duodenum in Case 1.



FIG. 2.—Large pituitary fossa in Case 1.



FIG. 3.—Pituitary fossa in Case 2 showing onesided enlargement, with evidence of calcium, probably in a cyst wall.

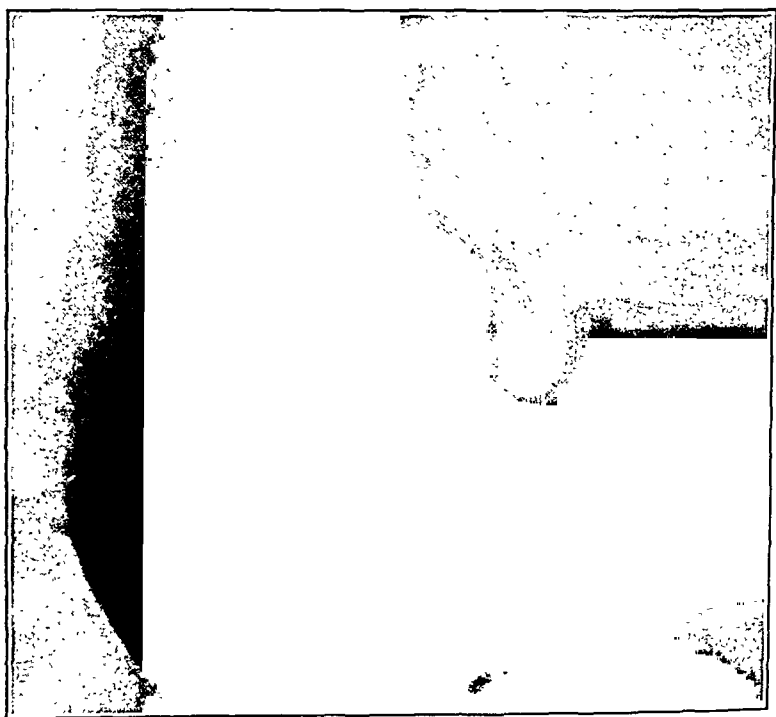


FIG. 4.—Large gastric ulcer, possibly malignant, in Case 2.

sometimes immediately after a meal, and at other times 3 to 4 hours later. Vomitus varied in quantity from a cupful to a pint. In addition, there was usually an ill-defined pain beneath the right costal margin, with a feeling of soreness in the upper abdomen. Heartburn was a frequent complaint. Appetite had always been good. Of special interest was her marked weight loss, from 152 to 111 pounds, in the 7 months before admission.

Past medical history included measles and mumps in childhood, scarlet fever at the age of 12, and pneumonia at 14. At 10 years of age, a Roentgen ray diagnosis of tuberculosis of the hip was made, and the patient was treated by immobilization with plaster casts. Family and social history was negative.

On physical examination one found a well-developed and well-nourished young woman, in spite of her marked weight loss. She was not acutely ill. Her intelligence was fair, and the patient was quite coöperative. There was slight bilateral exophthalmos and some lid lag. The thyroid gland was uniformly moderately enlarged. Blood pressure was 138 systolic and 76 diastolic. Examination of the lungs, heart, and abdomen was negative. There was moderate scoliosis to the right in the lumbar region, with greatly reduced tendon reflexes generally. Pelvic examination disclosed an exceedingly small uterus, one-fourth normal size, with a tiny cervix. Adnexa were not palpable. Pulse rate ranged from 80 to 115, and temperature was normal at all times.

Nothing significant was found in the routine laboratory studies which included complete blood counts, urinalyses, blood sugar, and blood Wassermann. Basal metabolic rate was +3 per cent. Stool examinations disclosed occult blood on a meat-free diet. Fractional gastric analysis revealed free hydrochloric acid up to 78° and total acid up to 108°. Because of the hyperacidity, vomiting, tarry stool, and weight loss, a gastro-intestinal Roentgen ray series was made by Dr. Henry K. Pancoast, who reported a penetrating ulcer in the beginning of the second portion of the duodenum.

After the patient had been 2 weeks on strict milk and cream diet and alkaline powders, Roentgen ray study showed: "Fluoroscopic phenomena were typical of duodenal ulcer. The films show a diverticulum-like structure projecting from the second portion of the duodenum, associated with a constant spasm and tenderness of the duodenum. The most likely possibility seems to be a perforated ulcer which has become walled off." Accordingly, laparotomy was performed by Dr. George P. Muller. A large penetrating ulcer was found, with a deep crater on the posterior superior surface of the duodenum, just below the pylorus. Exploration of the pelvis confirmed the presence of a small hypoplastic uterus. The gall bladder was normal in size, appearance, and consistency, and emptied readily on pressure. A posterior gastrojejunostomy was done, following which the patient made an uneventful recovery (Fig. 1).

In view of her amenorrhea and infantile uterus, a pituitary Roentgen ray was made, which Dr. Pancoast reported as follows: "There is a marked enlargement of the pituitary fossa with widening in the sagittal direction, and considerable atrophy of the dorsum sellæ. There is depression of the floor which is more marked on the left side. The measurements are: A. P. 15½ mm.; depth 17 mm. These measurements are distinctly abnormal and seem to indicate the presence of a pituitary tumor which has grown more on the left side than on the right" (Fig. 2). Spinal fluid pressure, cytology, and chemistry were found to be normal, along with the Wassermann and colloidal gold curve.

Following consultation with Dr. Francis Grant of the Section on Neurosurgery who concurred in the diagnosis of pituitary adenoma, it was felt that in view of the normal visual fields and the lack of symptoms, intracranial operation was not justified at that time. His recommendation of

intensive Roentgen ray treatment to the pituitary gland was followed (3 destructive doses being used). This treatment together with the administration of 2 ampules of "Theelin" daily for 1 week failed to inaugurate menstruation. Final diagnosis on discharge was: penetrating duodenal ulcer; pituitary adenoma; simple non-toxic goiter. This patient has been seen on February 15, 1933, and has no complaints except a very occasional attack of slight indigestion. She has gained 10 pounds in weight, has not yet menstruated, and presents no cut in the visual fields.

CASE 2 (No. 32-11576).—The patient was a white married male, aged 57 years, who was admitted to the Medical Clinic of Dr. Alfred Stengel in the University Hospital, September 13, 1932, with a chief complaint of sharp shooting pains in the legs and genitalia. He had been in perfect health prior to a year before admission, when he developed general malaise and lassitude, with dull aches in his bones. Simultaneously there appeared a widespread urticaria, with wheals which remained tender and painful for 10 days. About a week later the phalangeal joints of his left hand became painful and swollen. Coincident with this was the onset of sharp pains in the buttocks and posterior aspects of his legs. Three months before admission, terrific steady pains began in both legs, anteriorly, and in the genitalia. These pains were worse at night, or after sitting up for about an hour or more. They occurred practically every night until admission, and required analgesics for relief. During the past year, the patient suffered widespread loss of hair, especially from his arms, abdomen, and pubic regions. His nails became dry, wrinkled and brittle. Throughout his entire adult life, he had always preferred hot weather, and had gone to Florida for the winters. Now, even in warm weather, the patient always felt chilly. His appetite had always been ravenous, and he had no gastrointestinal complaints, except a mild constipation. History of other systems was negative except for a mild frequency and nocturia during the past several years. The patient had been married 40 years, but had no children. For the past 12 years, he desired and had no marital relations. He had become emotionally quite unstable following a recent loss of a large sum of money.

Past medical history included measles and whooping cough in childhood, and pneumonia in 1906. Family history was negative except for the death of his father from carcinoma of the stomach at the age of 61.

Physical examination on admission showed a short, stocky, white male, 64 inches tall, and weighing 168 pounds. The patient was intelligent, cooperative, and well oriented. Speech was slow and monotonous and rather husky at times. The skin was warm, dry, and of fine texture. The forearms, neck, and axillæ were somewhat pigmented. The scalp was partially bald, especially in the frontal region, and the remaining hair was dark, thin, and of fine texture, but not particularly dry. Pubic hair was thin and sparse, and the arms and legs were almost devoid of hair (patient states that until several years ago, he was quite hairy).

His features were coarse and broad, with a large nose, closely placed eyes, and a broad forehead. Tonsils were small and atrophic, and all teeth had been extracted. Examination of heart and lungs was negative except for distant heart sounds. Blood pressure was 122 systolic and 85 diastolic. Abdomen was negative. Prostate was of normal size and consistency; genitalia showed markedly atrophic and soft testicles.

The patient's hands were small and broad, with short, thick fingers. The nails suggested beaking, and were dry and brittle, with numerous longitudinal ridges. There was some limitation of motion of several of the phalangeal joints of the right hand. Tendon reflexes were normal, and no sensory disturbances were noted.

Routine laboratory data were negative, including a red blood count of

4,200,000, white blood count 7500, and hemoglobin 85 per cent (Sahli). Blood Wassermann was negative with all antigens. Other blood studies including serum calcium, cholesterol, uric acid, urea nitrogen, and fasting sugar, were normal. A glucose tolerance test gave blood sugar readings ranging from 85 to 126 mg. per cent following the ingestion of 100 gm. of glucose. Fractional gastric analysis was normal. Bleeding and coagulation time and clot retraction were normal. Orthodiagraphy showed a heart somewhat centrally placed, probably slightly enlarged, with a slight dilatation of the aorta. An electrocardiogram, reported by Dr. C. C. Wolferth, showed small *T* waves in Lead I and diphasic *T* waves in Lead II, with slurring of the *Q-R-S* complexes in Leads I and III. The *T* wave changes indicated myocardial abnormality, and were of the type that occur in myxedema. The basal metabolic rate was -22 per cent.

The clinical impression of some pituitary disorder was confirmed by Roentgen ray examination of the pituitary fossa, which was reported by Dr. E. P. Pendergrass: "Primary pituitary tumor with parasellar extension. There is a definite deformity of the sella turcica consisting chiefly of unilateral erosion. The appearance is indicative of a pituitary tumor, which is growing laterally into the middle fossa on one side. In this tumor there is evidence of calcium, probably in a cyst wall. On account of this, we believe that the lesion is probably a Rathke's pouch tumor" (Fig. 3).

Visual field studies showed a defect in the upper temporal sectors of each eye. Roentgen ray examination of the femur and right hand (taken to determine the cause of the severe pains in the extremities) was negative for any evidence of bone or joint disease. Pelvic Roentgen ray showed only slight hypertrophic changes involving the lower lumbar spine.

The patient was seen in consultation with Dr. Francis Grant who agreed with the diagnosis of pituitary tumor as evidenced by the patient's general make-up, the visual field cut, and the pituitary Roentgen ray. However, because of the lack of seeming relation of this with his chief complaint of pains in the muscles of his thighs, he did not advise cerebral operation at the time, and suggested Roentgen ray treatment to the pituitary. This was done but resulted in a severe reaction in the form of nausea and vomiting, with anorexia and headache. Dried thyroid substance was also given because of the lowered basal metabolic rate and coarse features, which suggested myxedema. This was discontinued because of the resulting nervousness and sweating.

The patient left the hospital for a month (October 22 until November 21, 1932). During his stay at home, his nausea and vomiting disappeared, but the pains in his legs and genitalia persisted. He had drunk about 2 quarts of water daily, had noted no change in vision, and appetite was good. On readmission, hemoglobin was 77 per cent, and Roentgen ray check-up on the pituitary fossa and visual fields revealed no change from previous examination. The outstanding complaints at this time were abdominal pain, nausea and vomiting, which, together with his marked weight loss (from 168 pounds several months previously to 124 at present), led to a gastric analysis and a gastro-intestinal Roentgen ray study. The latter disclosed a lesion on the lesser curvature of the stomach that was very suggestive of a large ulcer, possibly undergoing malignant degeneration. Treatment was attempted for peptic ulcer along the usual lines, together with preparation for the use of cortin, which was indicated because of the marked asthenia, hypotension (80/50 at this time), and slight bronzing—all together suggesting the syndrome of Addison's disease. However, the patient signed his release from the hospital, and died at home 10 days later. Permission for postmortem examination was refused (Fig. 4).

Final diagnosis was: Rathke's pouch tumor; gastric ulcer; possible Addison's disease.

Discussion. Recently Drouet and Simonin⁴ and Rappoport⁵ have reported good results in the action of pituitary extract in producing a marked diminution of gastric hyperacidity. These workers suggested that peptic ulcers might be benefited by pituitary extract therapy (puitritin). This is in accord with the findings of Cushing who showed that when puitritin is injected subcutaneously, it causes pallor without sweating, and promptly checks gastric peristalsis and secretion, its action being comparable to the effect of adrenalin. However, if puitritin is introduced into the cerebral ventricles, there is a marked acceleration of gastric motility and even retrograde peristalsis with vomiting. Thus, in both of the reported cases, it is not too fanciful to suppose that an excessive production of puitritin, the hypothetical autonomin,⁶ may have been instrumental in the ulcerative processes in the gastro-intestinal tract.

The work of Crile⁷ and McLaughlin⁸ is apparently not in complete agreement. Crile has claimed immediate relief from the symptoms of peptic ulcer and a decrease in the gastric acidity following bilateral denervation of the suprarenals, and McLaughlin, by adrenal damage, has produced peptic ulcer and has found no change in the postoperative over the preoperative gastric acidity (in the dog).

Peptic ulcers are commonly found in "high strung" individuals and it is a not uncommon clinical observation that the onset of peptic ulcer may follow definite psychic and emotional trauma. If puitritin is really the hypothetical autonomin bearing the same relation to the autonomic system as adrenalin to the sympathetic, a deficiency of this hormone or conversely an excess of suprarenalin may destroy the delicate body balance between the sympathetic and the parasympathetic, allowing an excessive adrenal action to produce spasms of bloodvessels and permitting erosions of the bloodless areas in the gastro-intestinal tract by the gastric or duodenal contents. An overactivity of the posterior lobe of the pituitary gland may lead to the formation of peptic ulcers either directly by the action of excessive puitritin liberated into the cerebral ventricles, or secondarily through suprarenal damage as is strongly suggested by the work of McLaughlin. The treatment of certain early cases of peptic ulcer by subcutaneous injections of puitritin seems worthy of trial.

Summary. 1. Two cases of primary pituitary tumor associated with peptic ulcer are reported. No similar cases have been found reported in the literature that were so diagnosed before death.

2. Inasmuch as lesions of the pituitary gland are always associated with disorders of the suprarenal cortex, and since recent experiments have shown that damage to the suprarenals will repeatedly produce intestinal ulcers (in animals), it is suggested that these 2 cases might supply the missing link in the chain of evidence support-

ing the alleged etiologic relationship between peptic ulcer and the endocrines.

3. Treatment of early cases of peptic ulcer by means of pituitrin subcutaneously seems worthy of trial.

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REVIEWS.

URINE AND URINALYSIS. By LOUIS GERSHENFELD, PH.M., B.Sc., P.D., Professor of Bacteriology and Hygiene and Director of the Bacteriological and Clinical Chemistry Laboratories at the Philadelphia College of Pharmacy and Science. Pp. 272; 36 illustrations. Philadelphia: Lea & Febiger, 1933. Price, \$2.75.

THIS is a book covering the normal and pathologic constituents of urine (with a brief discussion on the applied physiology of the kidney); the procedures of proven value, commonly used in chemical, microscopic, and bacteriologic urine tests; and various functional tests now in use. The author's long experience contributes valuably to pointing out in logical order where false positive and other sources of error may creep in. The subject of urinary crystals is adequately given and a modification of Heller's method of urinary calculi examination is included. At the end is an appendix of reagents and apparatus.

One is favorably impressed with the book's logical order and useful form and the author's indications throughout as to which test is best suited for precise results. Because of the clear interpretation of the tests this book is recommended to the clinician. Because of its improving influence it is recommended to the technician. This work is another step in bringing the clinician and laboratory worker closer together. J. B.

THE SCIENCE AND PRACTICE OF SURGERY. In two volumes: Vol. I, General Surgery; Vol. II, Regional Surgery. By W. H. C. ROMANIS, M.A., M.B., M.Ch. (CANTAB.), F.R.C.S. (ENG.), F.R.S. (EDIN.), Surgeon and Lecturer on Surgery, St. Thomas' Hospital, etc., and PHILIP H. MITCHNER, M.D., M.S. (LOND.), F.R.C.S. (ENG.), Hon. Surgeon to H. M. The King, etc. Pp. 1762; 752 illustrations. Fourth edition. Philadelphia: Lea & Febiger, 1933. Price, \$12.00 per set.

WITHIN a relatively short time this work has passed through four editions which in itself speaks well of its reception. The present edition has been thoroughly revised and greatly amplified, not only in the text but also in the illustrations. Each chapter on a region of the body is prefaced with a short account of the applied surgical anatomy and physiology of the region or organ discussed. Although the work discusses the recent advances in surgery, these are often too hastily done. Examples which might be given are "massive collapse of the lung" in which no reference to the position of the heart is given; and "death from burns," in which no mention is made of the important recent contributions on dehydration as a major factor in the cause of death. The discussion of shock and collapse can hardly be considered as having been brought up to date. It is chiefly in its physiologic implications that the work is not as yet up to date. The illustrations and the discussion of surgical technique are excellent. The surgical pathologic reviews are also well done. I. R.

THE RISE OF PREVENTIVE MEDICINE. University of London Heath Clark Lectures, 1931, delivered at the London School of Hygiene and Tropical Medicine. By SIR GEORGE NEWMAN, K.C.B., M.D., F.R.C.P., Hon. D.C.L., LL.D., Chief Medical Officer of the Ministry of Health. Pp. 270; illustrated. New York: Oxford University Press, 1932. Price, \$3.00.

THIS, the first lecture on the Heath Clark Foundation in the University of London for lectures on Preventive Medicine, appropriately gives a bird's-eye view of the origins of the subject. In its 10 chapters we read of: (1) Primitive man's conception of disease and how to prevent and treat it; (2) Hindu, Egyptian and Hebrew achievements; (3) Greek medicine and the Greek spirit; (4) how Greek medicine reached England through the Romans, Arabs and the Italo-Sicilian stream; (5) the futile struggle against medieval pestilences; (6) the Renaissance of anatomy and physiology (from Vesalius to Claude Bernard); (7) the clinical studies and achievements of more than a score of Britishers from Sydenham to Jenner; (8) the contributions of pathology and bacteriology; (9) the application of immunology, industrial and social hygiene, anesthesia and antisepsis; and finally, the organization of the British medical profession, and Department of Health, and the assistance given preventive medicine by an ever-extending humanism and public education. Today when prevention of disease is a deservedly popular slogan, a book such as this, instructive and entertaining, and written by a world's authority on his subject, should be warmly received.

E. K.

ROUNDAABOUT HARLEY STREET. The Story of Some Famous Streets. By CYRIL PHILLIPS BRYAN, M.B., B.Ch., etc. Pp. 260. London: John Bale, Sons & Danielsson, Ltd., 1932. Price, 5s.

THOUGH Harley Street may appear as "a long dreary artery which gives the impression of having been cut out of cardboard" to the Londoner familiar with the tangled streets of the older part of that great city, it stands out to us as the most celebrated medical street in the world. It and its only less famous neighbors, Wimpole, Wigmore, Welbeck, and Weymouth Streets, Portland Place and Cavendish Square constitute the medical quarter of London. High points in its history—chiefly medical—from the days of ancient Tyburn and Marylebone furnish the material for a narrative that is entertaining in the same way as is a walk through London's storied streets with a well-informed cicerone. Illustrations, which would have been especially apt for such a book, have been omitted, presumably from motives of economy; and we gratefully note the low price charged for an entertaining production.

E. K.

SYPHILIS DES HERZENS UND DER GEFÄSSE. By PROF. DR. ED. STADLER, Leitender Arzt der inneren Abteilung des Stadtkrankenhauses Plauen i.V. Vol. 16 of Medizinische Praxis, Sammlung für Ärztliche Fortbildung. Herausgegeben von L. R. Grote, A. Fromme, K. Warnekros. Pp. 82; 8 illustrations. Leipzig: Theodor Steinkopff, 1932. Price: Paper, Rm. 6.50; Cloth, Rm. 7.80.

THIS 16th volume of the "Medizinische Praxis" series (of which the 14th on Electrocardiography was recently reviewed in these columns) makes a practical presentation of cardiovascular syphilis quite different from what

would have been possible a short generation ago. Not only have pathologic and serologic advances demonstrated the frequency and increasing importance of the condition, but also treatment is now on an entirely different plane. The subject has been conservatively condensed, late syphilis of the aorta occupying about half the book, and summaries added to each chapter. Cardiac syphilis might perhaps have received fuller consideration, but the author is skeptical of Warthin's views, of independent syphilitic endocarditis and of the clinician's ability to make its diagnosis. The two pathologic illustrations present the main syphilitic features satisfactorily.

E. K.

CHEMICAL WAVE TRANSMISSION IN NERVE. Based on the Liversidge Lecture Delivered at Cambridge on May 13, 1932. By A. V. HILL, F.R.S., Foulerton Research Professor of the Royal Society; Honorary Fellow of King's College, Cambridge. Pp. 74; 13 illustrations. New York: The Macmillan Company, 1932. Price, \$1.25.

IN the compass of a single lecture, Professor Hill has correlated the chemical with the thermal and the electrical data bearing upon the transmission of the nerve impulse. Although the treatment is quantitative throughout, the use of mathematics has been restricted sufficiently to permit cursive reading. The time is apparently not yet ripe for definite conclusions to be drawn about the mechanism of transmission of the nerve impulse. A more complete mathematical treatment and brief description of technical methods has been segregated in three brief appendices.

G. McC.

THE COMMON COLD. ANNALS OF THE PICKETT-THOMSON RESEARCH LABORATORY, VOL. VIII. By DAVID THOMSON, O.B.E., M.B., CH.B. (EDIN.), D.P.H. (CAMB.), and ROBERT THOMSON, M.B., CH.B. (EDIN.). Pp. 738; illustrated, and 51 pages plates. Baltimore: The Williams & Wilkins Company, 1932. Price, \$15.00.

THE writers present a thorough abstract of the researches on the bacteriology, physiology and chemistry of the common cold, together with procedures used in its prophylaxis and therapy and valuable criticisms based on their own researches. To those interested in the bacteriology of the normal and pathologic respiratory tract, it is an especially valuable reference work. It is well written and should stimulate workers in this field to further bacteriologic and physiologic investigations.

J. C.

MANUSCRIPTA MEDICA. A Descriptive Catalogue of the Manuscripts in the Library of the Medical Society of London. By WARREN R. DAWSON, F.R.S.E., F.R.S.L., F.S.A. (SCOT.), Fellow of the Royal Society of Medicine (Vice-President, Section of History); Honorary Resident Assistant, Department of the History of Medicine, University College, London; Honorary Librarian of Lloyd's. Pp. 140. London: John Bale, Sons & Danielsson, Ltd., 1932. Price, 15s.

THE collection of 164 volumes of medical manuscripts in the Library of the Medical Society of London, dating from the 14th to the 19th centuries, is formed around the nuclei of the Askew, Sims and Lettsom collections. The author, who has written several volumes on medical historical subjects,

has here made these original sources of material available, believing with Garnett that "next to the importance of information existing at all is that of its being garnered, classified, registered, made promptly available for use." His numerous annotations and the index make it more than a useful record for historical students. E. K.

SYLLABUS OF MEDICAL HISTORY. By VICTOR ROBINSON, M.D., Professor of History of Medicine, Temple University School of Medicine, Philadelphia. Pp. 110; illustrated. New York: Froben Press, Inc., 1933.

THIS handbook contains specimen questions and answers from the author's course on the history of medicine at Temple University, together with a specimen essay ("Duchenne of Boulogne"), a specimen chronology (goiter), and specimen illustrations (prehistoric and Egyptian) from his lectures on the subject. There is also a useful chapter by Mr. Charles P. Fisher, Librarian of the College of Physicians, on the Photostat and its value to students. The book not only should make useful suggestions to those concerned with spreading knowledge of medical history, but affords beginning examples of activities that the individual student can easily and profitably carry further. E. K.

POLIOMYELITIS. A Survey made Possible by a Grant from the International Committee for the Study of Infantile Paralysis. Organized by JEREMIAH MILBANK. Pp. 562; 24 plates (1 in color); 82 tables and 19 charts. Baltimore: The Williams & Wilkins Company, 1932. Price, \$6.00.

THE rapidly advancing state of our knowledge of infantile paralysis and the number of problems still unsolved in its natural history render such a volume as this not only most timely, but even superior to a textbook treatment of the subject. The International Committee has been enabled by the generosity of Mr. Milbank to make such a complete and authoritative statement that "no medical library will be complete without this book." Of the 8000 references consulted, only those utilized in the book are included; those published by members of the committee being starred in the bibliography. In passing, one cannot but be curious about the needlessly clumsy method of referring to references in the text with letter and numeral (*e. g.*, M 37) instead of a consecutive number. Following a 23-page history, there are chapters on etiology, resistance and immunity, symptomatology, treatment, pathology and epidemiology—all excellent—by Drs. Harrington, Neal and Wells.

For students of the disease, such a book is indispensable and should set an example that could well be followed with respect to other baffling conditions. E. K.

THE VITAMINS IN HEALTH AND DISEASE. By BARNETT SURE, PH.D., Professor of Agricultural Chemistry, University of Arkansas, Fayetteville. Pp. 206; 4 tables. Baltimore: The Williams & Wilkins Company, 1933. Price, \$2.00.

A POPULAR treatise on the vitamins is very timely just now when general interest in the subject is so great. The vitamin story is one of the most interesting and understandable of the histories of scientific endeavor, and the author has retold it with success. He has, on the whole, stressed the

positive side of the good health to be expected from a well balanced diet containing an abundance of vitamins, and has included excellent tables of the vitamin content of a wide range of foodstuffs. On the relation of the vitamins to borderline pathologic conditions which are not the extreme avitaminoses we know as clinical entities, however, he has included much that is hypothetical, and would undoubtedly confuse the very readers to whom the book is addressed. As a text-book for undergraduates in introductory studies in nutrition, it would be of greater value if it contained more references to the classical researches in the vitamins. E. W.

KREISLAUFSTÖRUNGEN UND PATHOLOGISCHE HISTOLOGIE. By PROFESSOR DR. MARTIN NORDMANN, Privatdozent für allgemeine Pathologie und spezielle pathologische Anatomie an der Universität Tübingen. Pp. 174; 14 illustrations. Leipzig: Theodor Steinkopff, 1933. Price: Paper, Rm. 13.50; Cloth, Rm. 15.

THIS Volume IV of the *Ergebnisse der Kreislaufforschung* continues the general plan of treating monographically various phases of the large field of circulatory phenomena in health and disease. After preliminary historic and anatomic statements (26 pages), the work discusses under four headings: (1) the general pathology of local circulatory disturbances, and (2) of the peripheral circulation under various conditions; (3) general and (4) special pathologic histology of the human circulation. "General" is so widely interpreted that considerable space is given to edema, suppuration, necrosis, growth (2 illustrations of the Sandison-Clark window in the rabbit's ear) and so on. As a circulatory disturbance, Inflammation is given more detailed consideration than it receives in many a large text-book of pathology. E. K.

CLINICAL DIAGNOSIS, PHYSICAL AND DIFFERENTIAL. By NEUTON S. STERN, A.B., M.D. (HARVARD), Associate Professor of Medicine, University of Tennessee School of Medicine, Memphis. Pp. 364. New York: The Macmillan Company, 1933. Price, \$3.50.

THERE are two chief faults in student text-books of Physical Diagnosis: one of these is the attempt to include an abridged course in clinical medicine; the other is the emphasis laid on diseases of the heart and lungs at the expense of the rest of the body. This latter fault has commendably been avoided by the author. He has not succeeded as well with the former, so that the section on physical diagnosis contains serious omissions. The different kinds of râles and the mechanism of their production are neither fully described nor explained. The signs of pleural effusion are listed without mention of egophony, movable dullness, the Garland-Ellis line or Grocco's triangle. Little or nothing is said about the physical reasons for normal and abnormal signs obtained by palpation, percussion and auscultation of the lungs. S. L.

A TEXT-BOOK OF NEUROPATHOLOGY. By ARTHUR WEIL, M.D., Associate Professor of Neuropathology, Northwestern University Medical School, Chicago. Pp. 335; 260 illustrations. Philadelphia: Lea & Febiger, 1933. Price, \$5.00.

THIS excellent review of the present stage of our knowledge in neuropathology is readable, well illustrated and thoroughly modern in its view-

point. That much neglected stepchild of the medical specialties, neuropathology, seems to have come into its own. Weil discusses first the changes brought about in the nervous system through autolysis and fixation. This is a very valuable chapter, containing information otherwise not readily accessible. The next several chapters constitute an introduction to the general pathology of the nervous tissues, after which there is a systematic discussion of the special diseases commonly encountered. In an appendix is given a good summary of the essentials concerning the postmortem examination of the central nervous system which includes an account of modern methods used for histologic study. This book is a valuable addition to our literature.

B. L.

THE HEROIC AGE OF SCIENCE. The Conception, Ideals, and Methods of Science Among the Ancient Greeks. By WILLIAM ARTHUR HEIDEL, Research Professor of the Greek Language and Literature in Wesleyan University; Research Associate of the American Council of Learned Societies of the Carnegie Institution of Washington. Pp. 203. Baltimore: The Williams & Wilkins Company, 1933, for Carnegie Institution of Washington. Price, \$2.50.

THOUGH some three score Greek sages appear in the pages of this book, its emphasis is on the Heroic Age rather than on its heroes. The largest part of the work is devoted to the abstract concepts and ideals of Greek scientific thought and to a discussion of their scientific methods in order to indicate how the Greeks set about the task of laying the foundations of science. In the discussion of Observation, the first step in methodical scientific progress, it appears that the greatest progress was made in the very fields where observation played a minor rôle. The contributions of Menodotus and others to an Inductive Theory, the considerable utilization of Classification as a scientific method, and of Analogy and Experimentation are the other chief topics.

Though necessarily more difficult reading than a mere narrative of achievement—which the author deems impossible in view of the irretrievable loss of most of the creative works of the crucial period (600–100 B.C.)—this work will amply repay the reader for the time and thought spent upon it. It may even lead him to agree with Osler that “like everything else that is good and durable in this world, modern medicine is a product of the Greek intellect, and had its origin when that wonderful people created positive or rational science.” Its comprehension, like that of Johnson’s recent article (*Science*, 1933, 77, 569), would constitute an invaluable discipline for the budding scientist.

E. K.

OPERATIVE SURGERY. By ALEXANDER MILES, M.D., LL.D., F.R.C.S. (EDIN.), Consulting Surgeon, Royal Infirmary, Edinburgh, and D. P. D. WILKIE, M.D., F.R.C.S. (EDIN. and ENG.), Professor of Surgery, University of Edinburgh. Pp. 590; 321 illustrations. New York: Oxford University Press, 1933. Price, \$5.25.

A WIDE field of general surgery is covered in this book as well as operations on the brain and cord, orthopedic surgery, and other surgical specialties. The authors state that in this work “which replaces the companion volume of our Manual of Surgery, we have not attempted to cover all the

ground, but have been content to provide for the needs of undergraduates who require a guide to their studies in the class of Operative Surgery and in the hospital, and of young graduates who may be called upon to undertake operative work as house surgeons or in practice." Sixteen coadjutors have contributed in their special fields.

The majority of the procedures are illustrated with anatomic drawings. The descriptions are concise and clear and only the most generally used methods are discussed.

For the purpose for which it was intended this book should be most helpful.

I. R.

OPERATIVE SURGERY, VOL. VII. THE NEWEST OPERATIONS, GENERAL INDEX TO COMPLETE WORK, VOLS. I-VII. By WARREN STONE BICKHAM, M.D. and PHAR.M. (TULANE), M.D. (COLUMBIA), F.A.C.S., Junior Surgeon to Touro Hospital, New Orleans; Fellow of the New York Academy, etc., and CALVIN MASON SMYTH, JR., B.S., M.D., F.A.C.S., Assistant Professor of Surgery, Graduate School of Medicine, University of Pennsylvania; Surgeon-in-Chief, Methodist Episcopal Hospital; Visiting Surgeon, Abington Memorial Hospital. Pp. 849; 765 illustrations. Philadelphia: W. B. Saunders Company, 1933. Price, \$10.00.

THE supplementary volume of Bickham's Operative Surgery prepared by Dr. Smyth, is a welcome addition to this well known and useful thesaurus of surgical procedures. It aims to present the more important of the new and advanced operations which have secured recognition since publication of the original work. The selections have been well made. The descriptions and bookwork are of the highest order. The system has thus been rescued from the obsolescence which speedily overtakes all such works. The inclusion in the new volume of a complete general index incorporating the new material adds greatly to its convenience and utility. To those who already possess the System, the supplementary volume will be a necessity. To others it is not too much to say that Bickham is the leading American encyclopedia of operative procedures.

D. P.

PEPTIC ULCER. By JACOB BUCKSTEIN, M.D., Instructor in Gastro-intestinal Roentgenology, Cornell University Medical College; Associate Attending Gastro-enterologist, Sydenham Hospital, etc. Vol. 10 of *Annals of Roentgenology*, Edited by JAMES T. CASE, M.D., Professor of Radiology, Northwestern University Medical School. Pp. 417; 334 Roentgen ray studies, 77 clinical illustrations. Second edition, revised and enlarged. New York: Paul B. Hoeber, Inc., 1933. Price, \$12.00.

In this second edition Buckstein has greatly enhanced the value of his already noteworthy monographic atlas on peptic ulcer. Its chief merit lies in the elaborate series of beautifully reproduced roentgenograms, which illustrate every known type of so-called peptic ulceration of the stomach, duodenum, or jejunum. On the page opposite each illustration of a pathologic case is a brief but adequate description of such clinical, operative, autopsy and follow-up observations as are pertinent; also, pointed comment regarding the roentgenologic findings. The chapter on gastro-jejunal and jejunal ulcer is greatly amplified and includes illustrations to indicate the disappearance of the ulcer niche after treatment. Emphasis is placed on the Roentgen study of the gastric and duodenal mucosa under both normal and pathologic conditions. The book is not unnecessarily technical and will appeal to the clinician and surgeon as well as the roentgenologist.

G. M.

STUDIES IN THE HISTORY OF OPHTHALMOLOGY IN ENGLAND PRIOR TO THE YEAR 1800. By JAMES R. RUTSON, F.R.C.S. (ENG.), Consulting Ophthalmic Surgeon to St. George's Hospital and Senior Editor of the British Journal of Ophthalmology. Pp. 255; 9 plates. New York: The Macmillan Company, 1933. Price, \$4.00.

THOUGH this is largely a collection of papers published during the past decade by the author and the late George Coats, F.R.C.S., it presents a very fair picture of ophthalmology in England since the earliest times. The oculist's stamps of the Romans, the very extensive remedies of Anglo-Saxon leechdom, and the beginning study of optics by the three clerics, Robert Grosseteste, Roger Bacon and John de Peckham are the chief subjects considered up to the 14th century. John of Arderne's "de Cura Oculorum" and a few similar small treatises represent the next three centuries. With the Renaissance of science from the sterility of the Middle Ages, individual chapters have been devoted to the 17th and 18th centuries, yet more space is allotted to that famous quack, "Chevalier" Taylor and his family than to the previous eight centuries. While one cannot avoid the impression that a logical development of the subject has been handicapped by the method of presentation, yet a complete text on the subject was apparently not intended and most readers will probably find more of interest in the form here adopted. E. K.

LES RHYTHMES ET LA VIE. By M.-M. LAIGNEL-LAVASTINE, A. M. CHANOT, J. MONCHANIN, G. RICHARD, J. GUITTON, F. MENTRÉ, H. DUPRAT, H. CARDOT and R. BIOT. Pp. 264. Lyon: Librairie Lavandier, n.d. Price, 15 fr.

THE fact that in modern scientific research, specialized fact finding has outstripped collaboration and synthesis is one that is being steadily more appreciated by this generation. Such thoughts led the Groupe Lyonnais d'Études Médicales Philosophiques et Biologiques 8 years ago to try to lessen this defect by a series of publications, of which volumes on Sexuality, Heredity and Races and Forms, Life and Thoughts have already appeared. The present volume deals with rhythms, not only in the sense of phenomena exhibiting periodicity, but in the more intangible concept of the underlying fitness of things; thus permitting more than 100 pages to be devoted to the architecture of worlds, atoms and stars and the influence of the cosmos on human life. Of more concern to physicians are the chapters on microbic rhythms, and human neuromuscular, psychic, sexual, endocrine and social rhythms. Bearing in mind the limitations imposed both by the size of the volume and the aim of the series, the reader should find this an interesting and stimulating presentation. E. K.

URSACHEN UND BEHANDLUNG DER KRANKHEITEN (CAUSÆ ET CURÆ). By the AEBTISSIN HILDEGARD VON BINGEN. Translated by PROFESSOR DR. HUGO SCHULZ, Greifswald. Pp. 235. München: Verlag der Aertzlichen Rundschau Otto Gmelin, 1933. Price: Paper, Mk. 10.80; Bound, Mk. 13.

HILDEGARD, born in 1098 the youngest of 10 children of Hildebert Burgrave von Schloss Boeckelheim, was Abbess of the Benedictine nunnery on the Rupertsberge for 32 years before her death in 1179. A writer chiefly of theological works, but an observer as well, she wrote this "Causæ et Curæ" or "liber compositæ medicinæ" that contains the results both of her observations on the sick nuns and reading in the monastery library. Composed in the form of almost a thousand isolated paragraphs covering a wide

range of natural history, it affords an excellent picture of the culture of the period of the Crusades, influenced rather by the Galenism of Monte Cassino than the rapidly approaching Arabian tide. The creation of the world, the soul and angels, thunder and lightning, the sun and stars, each disposed of in a few lines, alternate with insanity, cancer, gout (p. 57), the healthiness of red blood (p. 224), the cause of fever, libido, why there are 4 humors, headache, cirrhosis (p. 366), worms in the teeth, and so on. The attributes of persons conceived in each of 30 months are given as many separate paragraphs. A number of topics are reverted to on several occasions—the fall of Lucifer apparently being a favorite—as if the book grew as a diary, recording the author's thoughts as they occurred, rather than in any systematic order. When she has finished she stops: "Hier hat dies Buch sein Ende, Den Schreiber niemand schände! Alle Kreatur sage: Amen!"

E. K.

BOOKS RECEIVED.

NEW BOOKS.

Diseases of the Nervous System. By W. RUSSELL BRAIN, M.D., D.M. (OXON.), F.R.C.P. (LONDON), Assistant Physician to the London Hospital and The Royal London Ophthalmic Hospital; Physician to the Hospital for Epilepsy and Paralysis, Maida Vale, etc. Pp. 899; 50 illustrations. New York: Oxford University Press, 1933. Price, \$8.75.

The Thyroid Gland. Its Chemistry and Physiology. By CHARLES ROBERT HARRINGTON, M.A., PH.D., F.R.S., Professor of Pathological Chemistry in the University of London. Pp. 222; 28 illustrations and 14 tables. New York: Oxford University Press, 1933. Price, \$4.50.

Arteriosclerosis. A Publication of The Josiah Macy, Jr., Foundation. By various contributors. Edited by EDMUND V. COWDRY, Washington University, St. Louis. Pp. 617; 86 illustrations. New York: The Macmillan Company, 1933. Price, \$5.00.

The Cyclopedia of Medicine. First seven volumes. (To be completed in 12 volumes.) GEORGE MORRIS PIERSOL, B.S., M.D., Editor-in-Chief, and EDWARD L. BORTZ, A.B., M.D., Assistant Editor. Chief Associate Editors: W. WAYNE BABCOCK, A.M., M.D., CONRAD BERENS, M.D., P. BROOKE BLAND, M.D., FRANCIS L. LEDERER, B.S., M.D., and S. GRAEME MITCHELL, M.D., CHARLES E. DEM. SAJOUS, M.D., LL.D., Sc.D., Founder and First Editor. Pp. 6322; amply illustrated with cuts and full-page black and colored plates. Philadelphia: F. A. Davis Company, 1931. Price, \$120.00.

The History and Epidemiology of Syphilis. The Gehrman Lectures, University of Illinois, 1933. By W. ALLEN PUSEY, A.M., M.D., LL.D., Professor of Dermatology Emeritus, University of Illinois, Some-time President of the American Dermatological Association and of the American Medical Association. Pp. 113; 37 illustrations. Springfield, Ill.: Charles C Thomas, 1933. Price, \$2.00.

St. George's 1733-1933. By J. BLONFIELD, O.B.E., M.D., Pp. 120; illustrated. London: The Medici Society, 1933. Price, 5s.

NEW EDITIONS.

A Synopsis of Surgery. By ERNEST W. HEY GROVES, M.S., M.D., B.Sc. (LOND.), F.R.C.S. (ENG.), Consulting Surgeon to the Bristol General Hospital; Emeritus Professor of Surgery, Bristol University, etc. Pp. 693; 164 illustrations, 13 colored plates. Tenth Edition. New York: William Wood & Co., 1933. Price, \$5.00.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Alcoholic Polyneuritis.—One of the interesting hypotheses concerning the pathogenesis of diseases has been the recent suggestion advanced by MINOT, STRAUSS and COBB (*New England J. Med.*, 1933, 208, 1244) that polyneuritis may depend upon a dietary deficiency. Comment has been made previously in this section that pellagra among alcoholics may be due to the indirect effect of the alcohol. There is the question not only of insufficient amount of B₁ but also in pellagra a hypothetical alteration in the gastro-intestinal tract, which apparently affects the absorption of the preventive vitamin, together with other factors that inhibit the effectiveness of the elements that prevent pellagra. Considering beriberi and polyneuritis there is a pronounced similarity between the symptomatology and pathology of the neuritis of these two conditions. With this idea in mind the Boston observers have studied 57 patients with alcoholic polyneuritis and in addition have gone over the records of 73 additional cases. Forty-three of the first group had careful dietary histories and gastric analyses performed; the latter group did not. The total 130 cases, however, give additional information for statistical purposes. All of these patients were alcoholics for a period of many years. Their average age was 44; approximately four-fifths of them were males. The onset of the symptoms showed a rather peculiar frequency during the hot months, contrary to the usual occurrence of deficiency disorders which have a predilection for the winter months. The dietary histories were obtained with difficulty. It was possible to formulate the usual diet of 43 patients from the families, friends and social service workers. Of this group only 2 had taken a diet which could be considered completely adequate. The remainder had eaten very little fresh food and very little protein-rich food for some years. It was not common to find that the total diet was not only inadequate in protein, mineral and vitamins but also in calories and the patients were subnourished. The food usually was almost entirely carbohydrate. Only 7 of the 43 patients had normal gastric secretion; 15 had a low free hydrochloric content and 21 had achlorhydria. The achlorhydria may be the result of an alcoholic gastritis. In true beriberi, the incidence of gastric anacidity is not greater than would be anticipated in the age group. The authors then compare associated deficiency disorders with beriberi, as for example, pellagra, the edema of protein want, hyperchromic anemia and true beriberi. They then point out that the symptomatology of alcoholic

polyneuritis is almost identical with descriptions of the dry form of beriberi as it occurs in the Orient. A pathologic comparison is likewise made between alcoholic neuritis and beriberi, although the comparison is not entirely adequate, due to the paucity of careful pathologic studies. In the treatment of the condition, 40 of the group of 57 patients were given a diet rich in proteins, minerals and vitamins with very little concentrated carbohydrate food. Cod-liver oil and yeast and iron were also added. It is impossible to make definite statement as to results of treatment, due to the absence of controls. In conclusion it is pointed out that alcohol may reduce the effectiveness of vitamins and that vitamin lack may be brought about by increasing the daily total metabolism. A quart of whiskey supplies 2800 calories, so that unusual demands for vitamins might develop, due to the increased metabolism induced by the alcohol. In other words the diets were deficient to start with just at the time when there was a greater need for vitamin B₁, owing to the increased metabolism. A comparison is drawn between the individual with subclinical beriberi whose symptoms may be precipitated by exercise. From these data the authors think it is fair to draw the deductions that lack of vitamin B₁ has an important rôle in the pathogenesis of alcoholic polyneuritis.

SURGERY

UNDER THE CHARGE OF

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Human Bite.—Wounds made by human teeth so frequently are followed by crippling end-results, that lesions which would at first appear to be minor are in fact a major problem in surgery. The patient usually regards the human bite as of little consequence while the bite of the dog, much less dangerous from the standpoint of local infection, usually causes great alarm. For this reason human bites are more likely to be neglected in the early stages, a time at which radical treatment is essential. In addition, a wound caused by human teeth is often incurred in a fight and for personal reasons the patient is prone to falsify the history of the injury. Even in cases where the correct history has been obtained and treatment begun early, the wound may appear so insignificant to the physician that conservative treatment is employed until such time as the infection and necrosis have become so widespread as to preclude satisfactory restoration of function.

An excellent clinical picture of the infection caused by a human bite has been presented in the splendid article on this subject by MASON and KOCH (*Surg., Gynec. and Obstet.*, 1930, 51, 591) which because of its clearness is here quoted.

“The patient, a young man, presents himself to a physician with a lacerated wound on the dorsum of the hand over one of the metacarpo-

phalangeal joints. The manner in which the wound has been received is frequently not disclosed and the possibility that the wound is due to a tooth injury therefore may not occur to the physician. After the wound is cleansed and the edges of the skin trimmed away, surgical closure is often made, and it may be thought wise to suture a divided tendon and close the joint cavity.

"Twenty-four or 48 hours later the patient again presents himself complaining of severe pain in the hand. The hand is then found to be considerably swollen. A lymphangitis may be present at this time, though it is by no means constant. The constitutional symptoms are not especially marked, but there is a moderate fever and a mild leukocytosis. The sutures, if any, are removed and hot wet packs applied to the hand, forearm, and arm.

"The pain subsides, but the swelling and fever persist and after several days it becomes apparent that drainage is inadequate and that lateral and proximal extension has taken place. By this time the secretion from the wound is moderately profuse and usually of a very disagreeable odor; if the true nature of the infection has not been disclosed it is now suspected. The original wound is opened more widely and found to communicate with the joint cavity. A considerable amount of grayish-brown fluid pus, exceedingly malodorous, is released. Similar pus is found in the soft tissues at either side of the affected joint and beneath the extensor tendon. Smears and cultures made from the pus show many organisms, among which may be the fusiform spirillum combination of Vincent. Drainage of the wound leads to a fall in temperature and an immediate though temporary improvement.

"Soon, however, there appears an induration in the palm, either over a lumbrical canal or over one of the larger fascial spaces, *i. e.*, the middle palmar, or, very rarely, the thenar space. These extensions require drainage, and at operation it is noted that with pressure on the dorsal and volar surfaces of the metacarpophalangeal joint purulent material can be expressed from the palmar incisions. At the same time or later the proximal phalanx of the affected finger also shows swelling and signs of exudate. The finger becomes swollen and indurated, painful on extension, and moderately tender. The tenderness is most marked over the two distal phalanges and no local pain over the course of the tendon sheath. The sides of the finger are incised, and more of the purulent exudate is released. The fibrous tendon sheath is seen to be intact though evidently inflamed, but the impression gained is that there is no pus within the sheath and it is not opened. From now on improvement takes place. The exuberant, edematous, weak looking granulations become more red and solid. The discharge becomes progressively less, the odor disappears and after several weeks or a month or more the wounds finally heal, leaving a stiffened finger.

"At irregular intervals following closure of the wound 'flare-ups' occur. These consist of acute inflammatory reactions, either on the dorsum of the hand under the original site of injury, or in the palm. These areas are incised and the inflammation subsides promptly under hot moist packs. Cultures from these foci may show fusiform bacilli; staphylococci and other organisms are usually present. This 'lighting-up' may be repeated several times before final cessation, and may occur as late as 18 months after the original injury (Case 2). In some in-

stances bone and joint involvement may have led to amputation early in the process."

In addition to supplying a classical description of the clinical picture of human-bite infections of the hand, these authors carried out experiments to determine the manner and degree of spread of material in various places in the hand which are commonly the site of the human bite. Of 13 cases of infections resulting from injuries caused by human teeth which were treated by Mason and Koch, 12 were males. The right hand was most frequently involved and in all but 3 instances the injury was received by striking another individual on the mouth. Incapacitation resulted in 1 instance for 7 months, 1 patient lost an arm because of ascending infection, but none of the 13 cases died. The authors point out that disability from infections of this kind must be reckoned in terms of months and weeks and not days, except where the infection has not been introduced below the fascial sheets of the hand.

Wounds from human teeth which result from fighting are most likely to occur over the knuckle and Mason and Koch point out that often the joint is penetrated while the hand is flexed, and when the fingers are extended the original line of entrance is sealed off by the skin and tendon as they move over the joint. With this type of injury, the infectious agent is introduced into the joint space, the dorsal subcutaneous space and the dorsal subaponeurotic space.

In regard to the primary treatment of human bites all authors agree that these should be considered as infected wounds and should not, therefore, be sutured. BATES (*Ann. Surg.*, 1931, 93, 641) is of the opinion that the wound should be cauterized thoroughly as soon as seen. Since 1920 he has been treating all penetrating human-bite wounds by completely burning out the whole tooth mark and, in avulsive or amputating bites, the raw surface is thoroughly seared with the cautery. Patients seen as late as the 4th day after the injury and with extensive infection are treated similarly, even if all the infected tissue cannot be removed. Bates has treated over 100 cases of human bites in this manner and he reports but 1 case in which there was an extension of the infection. Only 2 of the patients required hospitalization. Extensive cauterization of a benign appearing wound may appear radical but the low incidence of crippling infection and hospitalization which Bates reports would appear to make this type of treatment attractive. OWEN (*Ann. Surg.*, 1931, 93, 781), however, "has not been able to get the same results as Doctor Bates with the cautery, but perhaps did not try it sufficiently. He has tried everything; one of the main things he has had to contend with is internes sewing these wounds up without drainage. He always opens the wounds widely under gas anesthesia. Exposed metacarpophalangeal joints in these cases show rapid destruction of the cartilage, probably because the impact is one of the cartilage originally and because of the poor blood supply. Infection and ankylosis of the metacarpophalangeal joint often occur."

The organisms which have usually been thought to cause the widespread infection and necrosis resulting from human bites are the fusiform bacilli and spirillum found in cases of Vincent's angina. This combination of organisms is commonly present in the human mouth and it is reasonable to assume that wounds inflicted by human teeth

should contain these organisms. However, these organisms are not the only organisms which are present. The bacteriologic studies on the cases reported by Mason and Koch indicate that most human bite infections are the result of a mixture of organisms. The organisms are not solely responsible for the extent of the infection which follows. The trauma associated with the injury, the fact that the wound is a penetrating one which often enters the joint, and the anatomical relationship of the structures over the knuckles where most of these wounds occur are additional factors which make these wounds difficult to handle if not treated actively and early.

THERAPEUTICS

UNDER THE CHARGE OF

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Sodium Evipan for Intravenous Narcosis of Short Duration.—The sodium salt of the newly synthesized evipan (C-C-Cyclo-hexenyl-methyl-N-Methyl-barbituric acid) is readily soluble, suitable for intravenous injection and possesses properties suggesting its suitability as an anesthetic of short duration. As a result of these facts, WEESE (*Deutsch. med. Wchnschr.*, 1933, 59, 47) reports a series of pharmacologic investigations of this drug. Employing a 10 per cent solution he finds that narcosis begins within the first 1 to 2 minutes of injection, its development being smooth, uniform and without an excitation stage. Respiration becomes slower and deeper but remains regular and there is no evidence of circulatory depression. Fatal doses kill by respiratory standstill. The only observed side action is a tendency to the development of fine muscular tremor and fibrillating contractions. For cats the effective narcotizing dose lies between 20 and 30 mg. per kg., whereas the fatal dose lies between 100 and 110 mg. Doses of 20 and 25 mg. per kg. produce a narcosis lasting about 10 minutes at a depth between the 3d and 6th stage, and complete recovery takes place within 30 to 60 minutes. With doses of 30 mg. the average duration of the 3d stage is 49 minutes and the average time of recovery 180 minutes, while with doses of 60 mg. per kg. deep narcosis lasts for 1 hour and recovery appears on the average after 370 minutes. There is a slight and unimportant fall in blood pressure following narcotic doses. The drug injected subcutaneously is not irritant to the tissues and intravenously it does not tend to produce thrombosis. There is no hemolysis produced by the drug. It may be preceded with safety by the administration of morphin which reduces somewhat the size of the narcotic dose of evipan sodium. The drug is not excreted as such but apparently is destroyed in the liver at a very rapid rate.

BAETZNER (*loc. cit.*, p. 48) reports upon his clinical experience with evipan sodium in a series of 400 patients to whom the drug was administered without a single instance of serious disturbance. He recommends it as a preliminary and supplemental narcotizing agent with which ether or ethyl chlorid may be safely employed. He recommends slow intravenous injection lasting from 60 to 90 seconds and points out that the patient should be completely prepared for operation before injection is begun because anesthesia begins so promptly, usually within 1 minute of the beginning of injection. The average dose for an adult lies between 8 and 10 cc. of the 10 per cent solution but no fixed rule can be given and there is no definite relationship of the dose to body weight or other similar factors. The dose is best gauged by administering slowly a quantity just sufficient to induce quiet sleep which will last less than $\frac{1}{2}$ hour. If the operation is to be more prolonged than 10 or 15 minutes, 2 or 3 cc. more of the solution should be injected after the minimal dose required for sleep has been given. Many operations can be carried out completely without supplemental inhalation anesthesia and the author observes satisfactory muscular relationship even for laparotomy. He recommends for major operation, especially in elderly patients, that a preliminary dose of morphin and atropin be given, although the author feels that this may well be unnecessary and that further investigation is required to determine whether or not it is of real value. He finds that elderly patients and those who are exhausted by severe illness, loss of blood, fever, septic conditions and cachexia generally require smaller doses than the average individual. He also recommends that prolonged anesthesia may well be accomplished with safety without the danger of overdosage if subsequent small injections of evipan be administered when the patient shows signs of awakening. In this way he has kept patients anesthetized for periods of time up to $2\frac{1}{2}$ hours and has employed total quantities up to 16 cc. of the solution. While the drug is useful as a very quick basic anesthetic or as the only anesthetic, even for prolonged major surgical operations, its chief virtue seems to lie in its rapid and complete destruction so that it is especially suitable as a fixed anesthetic for operations of short duration.

HOLTERMANN (*loc. cit.*, p. 50) reports upon his experiences with evipan sodium as a narcotic for gynecologic operation and in childbirth. He advocates individualization in dosage and agrees in general with the preceding author as to the average dose required. His experience covers some 700 cases, three-quarters of which required gynecologic operation, and he finds the drug generally quite satisfactory in the majority as a complete narcotic, supplementary narcosis by inhalation being required in only about one-fifth of the patients. He, too, finds it especially valuable for operations of brief duration. He feels that in obstetrics its special value is as a brief anesthetic for necessary surgical procedures following delivery and does not recommend it as a complete narcotic for delivery itself because of its interference with uterine contraction and of its depressant action on the higher brain centers of the child. In his experience he has observed no serious side actions or after-effects, the only ones seen being slight muscular twitching and at times headache, temporary hiccoughs and brief periods of weeping.

PEDIATRICS

UNDER THE CHARGE OF
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An Appraisal of Antirachitics in Terms of Rat and Clinical Units.
—HESS and LEWIS (*J. Am. Med. Assn.*, 1933, 101, 181) as a result of their studies have come to the conclusion that an irradiated milk, which contains 56 units to the quart suffices to protect infants against rickets when from 20 to 24 ounces daily are fed. This indicates that the protective dose is from 35 to 42 rat units. From their experience with yeast milk they conclude that this type of milk should be elaborated so that it will contain from 90 to 100 units per quart, in order that the infant will receive about 7 rat units per day. With viosterol, their experience was not so satisfactory, and they were unable to set down a dosage with the same degree of definiteness. From their observations 600 to 800 rat units of viosterol should be given in order to afford adequate protection. This means 8 to 10 drops of an 80 unit preparation (250 D). They feel that viosterol is the best antirachitic agent of all for curative purposes if given in adequate dosage. The study included a clinical appraisal of cod-liver oil in $\frac{1}{2}$ teaspoonful and in 1 teaspoonful doses. The results were somewhat irregular and unsatisfactory. The preparations that they assayed clinically, when titrated biologically in two laboratories, were found to contain from 37 to 40 rat units per gram. This conforms to the results observed by several agencies, including the Bureau of Standards. In summing up their experiences with oil of this potency, it would seem that there is considerable variation in susceptibility to rickets and in the individual requirements of the antirachitic factor.

The Tuberculin Patch Test: A Diagnostic Aid in Tuberculosis.—GROZIN (*Am. J. Dis. Child.*, 1933, 46, 17) describes the tuberculin patch test as being made by moistening a piece of adhesive plaster with 1 or 2 drops of tuberculin and applying it to the skin, which has been cleansed previously with ether. For a control, a piece of adhesive plaster without tuberculin may be used. A positive reaction results in redness studded with papules and vesicles. In his observations on 176 cases the author was convinced that this method compared favorably with the Pirquet test as to reliability. There are a number of advantages over the Pirquet and other methods. It is absolutely painless. It requires no boring scratching or rubbing. It requires no sterilization of instruments. There is no danger of infection. It is of the simplest technique, and may be performed by nurses without special training. It is less time consuming, as it is not necessary to wait for the tuberculin to dry, and it is not necessary to watch the child so that it does not wipe off the tuberculin or spread it to the area of control. For this reason it is advantageous where large numbers of tests must be performed. It is possible to control the limit of the area of reaction since this is usually restricted to the area covered by the adhesive plaster.

It is easier to interpret the result with the tuberculin patch test because the area of reaction can be enlarged arbitrarily by applying larger pieces of adhesive plaster, more tuberculin and tuberculin of greater concentration.

Ten Years' Observation of Children With Rheumatic Heart Disease.—STROUD, GOLDSMITH, POLK and THORP (*J. Am. Med. Assn.*, 1933, 101, 502) studied 458 children in a convalescent hospital. The average age of the patients at the primary manifestation of rheumatic fever was 7.3 years. Of the 307 (54.8 per cent), who have been followed up, 125 (40.7 per cent) are dead or totally disabled, and 182 (59.3 per cent) are working or able to work or go to school. In order to get definite information as to the incidence of colds, sore throats and other infections of the respiratory tract in other members of the family and their relationship to primary manifestations and reactivations of rheumatic fever, the problem and its importance must be explained carefully to the children and their parents as well as to each member of the family. The most practical form of prophylactic treatment at the present time is the taking of measures to protect the children with rheumatic heart disease from the common cold and other infections of the respiratory tract both theoretically and practically. The use of intravenous injections of preparations of hemolytic streptococci with the hope of lessening hypersensitiveness is still in the experimental stage, but there is an indication that it may be of some value. Of a total of 428 primary manifestations and reactivations of which there was positive information, 61 per cent occurred between the months of December and May, with a peak of 65 (15.2 per cent) during March. During these months the prophylactic measures are of the utmost importance, especially in susceptible children between the ages of 6 and 10 years. Racially the greatest number occurring according to frequency are of Italian, Hebrew, American and Irish parentage. The familial incidence as high as that in tuberculosis was noted. Although there was no definite proof that the routine removal of tonsils prevented primary manifestations or decreases reactivations of rheumatic fever, this procedure, in conjunction with a careful consideration of the sinuses, is highly recommended. In this group premature contractions were found with relative infrequency, and auricular fibrillation, when found, was usually terminal or close to death. The prognosis was found to be little influenced by the particular valve or by the number of valves involved in rheumatic heart disease in childhood, but the virulence of the infection, the resistance of the host and the number of reactivations were of more importance in prognosis.

Acute Leukemia in Children.—COOKE (*J. Am. Med. Assn.*, 1933, 101, 432) in reference to treatment says that the effects of blood transfusion varies greatly in different children. In some definite improvement continued for a week or more after transfusion, and it could be repeated several times, while in others few effects could be observed. The tendency to continued severe hemorrhage was often countered temporarily by transfusion. In general the transient effect and the certain eventual outcome of the disease made the use of transfusions of doubtful value. They produced no change in the leukocyte picture, not even a tempor-

ary increase in granular cells. The few children with leukemia treated by Roentgen irradiation did not improve, and certain of them seemed more toxic after such treatment and died in a short time. The impression gained was that irradiation is contraindicated. In only one group was such irradiation of value. This was in children who had massive mediastinal infiltration producing compression of the trachea and vessels with dyspnea. In this group irradiation produced an almost immediate disappearance of the mediastinal tumor and of the compression symptoms in the patients in whom leukemic blood changes had not appeared, although the leukemic picture developed from a few weeks to several months later. On the other hand, in children in whom irradiation was employed after the characteristic blood picture was present, it was without benefit. The opinion has been expressed that such patients with mediastinal tumors but without leukemic blood changes really have mediastinal lymphosarcoma which was transformed into leukemia by the irradiation. This does not seem quite likely because of the large number of instances of massive mediastinal infiltration in which acute leukemia develops without irradiation. Many patients with mediastinal or other lymphosarcoma receive irradiation without the least appearance of leukemic change. Other patients are ill for more than a month with symptoms referable to the leukemic state but without the leukemic blood picture, but in whom a leukemic blood picture develops without previous irradiation.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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The Use of Extract of Spleen in Certain Dermatoses.—Following the observation of Ehrlich that eosinophilia developed in splenectomized animals, von Zumbusch investigated the problem clinically, followed by the work of Mayr and Moncorps who injected subcutaneously an albumin-free extract of hogs' spleen into a group of patients who had itching dermatoses associated with eosinophilia and reported diminution in eosinophils, decreased itching and general improvement. The literature dealing with the use of splenic extract in dermatoses is reviewed by WIEN and PERLSTEIN (*Arch. Dermat. and Syph.*, 1933, 27, 963), who report their study of the use of this product in 50 cases; a group of 25 patients with eczema and a second group which included cases of seborrheic dermatitis, infectious eczematoid dermatitis, secondary toxic exfoliative dermatitis, urticaria and dermatitis herpetiformis. The method utilized by the authors is the daily subcutaneous injection of 2 cc. of a 500 per cent purified aqueous extract of hog spleen for 7

injections, followed by injections on alternate days during the second week and 2 or 3 times weekly during the 3d and 4th weeks, depending on clinical response. Pain at the site of injection is the most frequent reaction. Less commonly general reaction was noted with fever, chill and general malaise appearing 12 to 18 hours after the injection and subsiding within 24 hours. Splenic extract in the authors' experience was of distinct value in urticaria, dermatitis herpetiformis and secondary toxic exfoliative dermatitis. The clinical response varied from a complete cessation of itching with disappearance of lesions to only a diminution of pruritus. It has limited usefulness in the temporary alleviation of certain phases of eczema, tending to decrease pruritus and shorten the period of acuity. The results in a group of patients with the eczema-asthma-hay fever complex were unsatisfactory, the only benefit noted being temporary relief from itching. The authors are unable to support the enthusiastic claims made by a few observers, but believe splenic extract worthy of further investigation and a valuable method of trial in resistant dermatoses.

Relapsing Febrile Non-suppurative Panniculitis (Weber).—An exhaustive case history of this rare condition characterized by the appearance of painful nodules in the subcutaneous fatty tissue is presented by ALDERSON and WAX (*Arch. Derm. and Syph.*, 1933, 27, 440). Clinically the lesions at times have the appearance of erythema nodosum. Pathologically they must be differentiated from adiposus dolorosa, Darier-Roussy sarcoid and erythema induratum. The outstanding microscopic findings in panniculitis are: (1) Extensive replacement of the fat cells by fibroconnective tissue; (2) large numbers of lipophages and giant cells with their foamlike protoplasm; (3) freedom of the epidermis and corium from involvement at any time, and (4) absence of hemorrhage and pigment formation. While the etiology of panniculitis is not established, "toxins" or bacteria may be causal as suggested by the frequency of fever, arthritis, and toxic erythema. Various forms of local trauma may also be productive of this form of fat atrophy as noted following injections of insulin, hypertonic dextrose, and saline and narcotics.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Simple Test for Cervical Cancer.—All gynecologists are agreed that in order to obtain the best results in the treatment of cancer of the cervix it is essential to recognize these cases in their early stages. In an interesting paper GRAVES (*Surg., Gynec. and Obstet.*, 1933, 56, 317) states that he has had much satisfaction in the early diagnosis of cancer

of the cervix from the use of the Schiller test. This test is based on the fact that the upper layers of the normal epithelium of the portio and the vagina are rich in glycogen which disappears when the epithelium becomes cornified or changed by cancer. In the normal living tissue the glycogen of the upper layers of cells is stained in a few seconds a deep mahogany brown by iodine in watery solution (Lugol's solution). A superficial area of early cancer being devoid of glycogen does not receive the stain and stands out startlingly white or pink against the deeply colored background of normal tissue. While the test is simple it is not without its limitations. It appears to be completely reliable when it is clinically negative, that is to say when all the tissues take the normal stain, therefore the test is specific in the *absence* of cancer in the areas to which the iodine has been applied but there are several conditions that obscure the test and with these the examiner should be thoroughly familiar. The stain does not take on glandular epithelium like that of the endocervix, hence an eversion would appear pink and an adenocarcinoma, which fortunately is rare, would not stain. Ulcerations and erosions have no epithelial covering of the squamous type and hence do not stain. In areas of chronic cervicitis the epithelium is often deficient in glycogen, taking a very light brown stain which blends with the surrounding deeply staining tissue instead of being sharply defined from it as in cases of cancer. It is also important to remember that the normal stain is prevented or obscured by slight trauma such as that from tenacula or scrubbing with gauze. This is caused by the rubbing off of the upper layers of epithelium which contain the glycogen. The cervix and vagina of the hypoplastic and atrophic individual stain lighter than the normal but during pregnancy the stain is especially deep. Pus stains black but living granulations do not take the stain while mucus, blood and douche water obscure the reaction. Hyperkeratosis prevents the stain as in leukoplakia, lues and exposed areas in prolapse. The test is of value only in cervical cancer and is not adapted to other superficial cancers such as those of the vulva and skin in other parts of the body. This is due to the fact that the epidermis of the portio and vagina is not cornified and that the upper layers of cells contain a special chemical type of glycogen. We have previously called attention to this test when it was reported by Schiller in the German literature and we believe that the enthusiastic report of such a careful observer as Graves gives much support to Schiller's claims. Since the test is quite simple in performance and easily interpreted it would seem that it should be of great value to the general practitioner as well as the specialist in detecting cervical cancers when they are still in the microscopic stage and therefore in the optimum stage for treatment. (It is also of value in indicating areas from which biopsy specimens should be secured—C. C. N.)

Quinin Treatment of Trichomonas Vaginitis.—In recent years much consideration has been given to the form of vaginitis which is due to the presence of the *trichomonas vaginalis*. While the disease is frequently found it is often refractory to all of the treatments which have been suggested. Since the organism is a protozoön and since quinin is an agent which frequently destroys some of the protozoa it occurred to SURE and BERCEY (*Am. J. Obstet. and Gynec.*, 1933, 25, 136) that this

cinchona alkaloid might be useful in the treatment of such cases. In their small series of 7 cases all have been improved clinically and microscopically by the use of quinin although 6 of the patients had previously received various treatments without improvement. The treatment merely consists of the insufflation of 15 grains of quinin sulphate powder into the vagina with a powder blower daily for a few days, checking the effect of the drug on the organisms which as a rule soon disappear. In some cases this was supplemented by the use of 15-grain quinin capsules which the patient inserted into the vagina at night. Under the microscope it was found that when quinin was brought in contact with the trichomonads they were immediately thrown into a spasm followed by diminishing motility with complete cessation in a short time. While this series is quite small, the treatment is so simple and harmless that it would seem that it is worthy of trial by other observers in the treatment of this annoying disease.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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The Peripheral Vascular System of Glaucoma Patients.—MÉSZÁROS and TÓTH (*Klin. Monatsbl. f. Augenh.*, 1933, 90, 67) investigated the peripheral vascular system of 22 patients with chronic simple glaucoma, of 2 with acute inflammatory glaucoma and of 1 with chronic inflammatory glaucoma. The ages of the patients varied from 35 to 74 years. Special studies were made of the blood pressure, of the reactive hyperemia time of the fingers, of the pressure in the vessels of the skin and of the capillaries at the nailfold, on the back of the hand, in the mucous membrane of the lip and in the conjunctiva. The blood pressure was above normal in 17 of the 25 patients. The reactive hyperemia time was delayed in 92 per cent of the cases. The pressure in the vessels of the skin was below normal in 10 of the 14 cases in which it was measured. The capillaries showed dilatation, especially of the venous loops, and often also spastic constrictions and circumscribed dilatations in the venous capillaries. The speed of blood flow was definitely slowed in all cases and some cases showed stasis at times. Apparently the peripheral vascular system of hypertensive patients with glaucoma is more affected than that of hypertensive patients without glaucoma. Also, the peripheral vascular system of glaucoma patients without hypertension is definitely pathologic. The type of capillary involvement is similar to that seen in vasomotor neuroses. The grade of delay in the reactive hyperemia is similar to that seen in severe vasomotor neuroses or organic vascular disease such as arteritis obliterans or scleroderma. The authors conclude from their investigations that

vascular spasms, especially involving the venous system of the eye, are of considerable importance in the causation of glaucoma since they can give rise to stasis and rise of tension. A slowly, gradually developing spastic condition of the veins would lead to chronic simple glaucoma. A suddenly developing, marked venous spasm would produce acute inflammatory glaucoma. Primary glaucoma seems to be definitely connected with a vasomotor neurotic type of disease of the peripheral vascular system.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Relation of Vitamins A, D, B and G to Otolaryngology.—After a comprehensive review of relevant literature, CODY (*Arch. Otolaryngol.*, 1932, 16, 661) reports results of personal experimental investigations on 70 albino rats, and of his clinical observations having to do with the effect of a deficiency in vitamins A, D, B and G on the ear, nose and throat. Verbatim, Cody's conclusions are: Vitamin A is necessary to maintain the nutrition of the nasal, aural and tracheal epithelia. The nasal mucosa is affected before, and recovers after, the ocular mucosa. Eventually the metaplastic and inflammatory changes of the deficiency are cured by a normal diet. Prophylactically, vitamin A seems to increase the resistance to upper respiratory infection in children. Therapeutically, its chief value is to improve the nutrition of the nasal and aural mucous membranes in acute and chronic infections. While this avitaminosis may be an etiologic factor in atrophic rhinitis, further investigation is required before deciding its status. A diet deficient in vitamin D has no effect on the nasal, aural and tracheal mucosa. It produces no lesion in the osseous labyrinth in the rat that resembles otosclerosis in the human being. Deficiency in vitamin B is identified with a definite nasal syndrome. This consists essentially of a postnasal mucous discharge, and the posterior tips of the middle turbinates are smooth, moist, creamy white and slightly thickened. Deficiency in vitamin G has no effect on the ear, nose or throat.

Variations in the Temperature of the Mucous Membrane of the Nose.—The clinical observation of thin nasal mucosæ in patients with a high basal metabolic rate, and of edematous mucosæ (as seen in allergic states) in those with a subnormal metabolic rate, suggested to CONE (*Arch. Otolaryngol.*, 1933, 17, 65) an investigation to determine possible intranasal temperature variations similar to the thermal changes of the extremities in such conditions as Raynaud's and Buerger's disease. To this end, simultaneous oral and nasal (inferior turbinate) temperature readings were made by means of a dermaterm with a specially designed intranasal attachment. The results obtained from 75 cases are divided into 5 groups, which presented the following average nasal temperatures: (1) Normal, 32° C. (89.6° F.); (2) acute rhinitides, 33.8° C. (92.8° F.); (3) hyperthyroidism, 32.5° C. (90.5° F.); (4) hypo-

thyroidism, 30.4° C. (86.7° F.); and (5) allergic, 31.1° C. (87.9° F.). Thus it will be seen that patients with acute nasal infections and high basal metabolic rates yielded nasal temperatures above normal. Whereas the reverse was true in patients with subnormal metabolic rates and with nasal allergic states. Moreover, in patients with unilateral edema, the temperature was lower in the edematous nostril. Contrariwise, in cases with unilateral infection the thermal reading was high on the affected side. The author concludes that "The changes in temperature in patients with abnormal basal metabolic rates, vasomotor rhinitis and allergy may be due to the variations in the sympathetic vasoconstrictor activity, as evidenced by the changes in color, volume and temperature of the turbinates."

Electrical Currents Associated With Sound Reception by the Ear.—The remarkable phenomenon of the reproduction of voice sounds and musical tones entering the cat's ear, by amplification of electrical currents from the eighth nerve and neighboring structures, observed by WEVER and BRAY (*Psychol. Rev.*, 1930, 37, 365) has been confirmed by others. If the view held by the discoverers of this phenomenon is substantiated, that these currents represent true action currents related to hearing, it will necessitate a marked revision of our present views in regard to the refractory period and frequency of impulse transmission in sensory nerves, or else the assumption of an elaborate coordinating mechanism. BAST, NOER, WEST, BACKUS, KRASNO and EYSTER (*Proc. Soc. Exp. Biol. and Med.*, 1933, 30, 638) have found the same phenomenon in the dog under sodium barbital or nembutal anesthesia. Using a 6-stage amplifier sufficient volume was produced to obtain clear phonographic reproduction of words, sentences and single frequencies between 100 and more than 5000 per second. After summarizing their results—in part confirming, in part supplementing, and in part contrary to previous observations—the authors state that if these currents arise from cochlear microphonic action, this apparatus is not a simple resistance microphone, inasmuch as a condenser in the input circuit to the amplifier, reducing the small constant grid current to zero, is without effect. They have evidence that the basic process may be of the nature of streaming potential. "The origin of these currents, and their relation if any to hearing requires further investigation."

RADIOLOGY

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Roentgen Diagnosis of Lesions in the Small Intestine.—In attempting to make the diagnosis of small intestinal lesions SOPER (*Radiology*, 1933, 20, 76) considers the technique to be of extreme importance. First, the patient must be examined in the upright posture. Second,

begin to look for abnormalities in the small intestinal pattern from the 2½- to the 6-hour period. They are often encountered just about the time the last part of the barium meal leaves the stomach. Third, secure a film of the suspicious area at once and continue to look for other overfilled loops. The shadows are apt to be evanescent; it is a mistake to expect them to be persistent. In cancer of the small intestine the dilated loop is usually irregular in contour and is surmounted by a small gas bubble. The test for occult blood is positive in nearly every case of malignant disease of the small bowel. Diverticulum of the small intestine is usually of smooth contour and is rarely surmounted by a gas bubble.

Roentgen Diagnosis and Localization of Opaque Foreign Bodies in the Air Passages.—According to MANGES (*Am. J. Roent. and Rad. Ther.*, 1933, 29, 368), foreign bodies are more often swallowed than aspirated, but most of those which enter the air passages remain there, and not more than 2 or 3 per cent are expelled by coughing. It is remarkable that such patients, especially children, are often permitted to go for months or even years without a Roentgen examination. This examination should comprise both antero-posterior and lateral views, for foreign bodies may lodge in bronchi behind the heart. The examination should include all the air passages from the nasal chambers to the depth of the lungs. Most foreign bodies, particularly those which are opaque, are found in bronchi of the lower lobes. Tacks and nails are nearly always found with the heads downward. Screws, on the other hand, usually have the points downward. Safety pins constitute about 12 per cent of all foreign bodies. The majority are open with the open end uppermost. Localization should be made just prior to bronchoscopy, because a certain percentage of foreign bodies shift from one branch to another.

Factors Influencing the Types of Metastatic Carcinoma of Bone.—Metastatic lesions in bone are commonly classified as osteoplastic or osteoclastic, depending on the relative degree of production or destruction of bone in the area affected, and numerous hypotheses have been advanced to explain the difference in the effect produced. DOWNS and HASTINGS (*Am. J. Roent. and Rad. Ther.*, 1933, 29, 1) have conceived a theory that primary tumors which stimulate the growth of connective tissue will exercise the same stimulus in the metastatic lesions which they produce, and that, commonly, highly cellular tumors without the power of exciting desmoplasia will produce osteolytic metastasis. Accordingly the authors have tabulated a series of cases which tend to confirm the theory, although there are numerous exceptions. Most of the adenocarcinomas, and the medullary, epidermoid and simple carcinomas gave rise to destructive metastasis, whereas most of the scirrhous carcinomas produced osteoplastic metastasis. It is noteworthy that the earliest metastatic lesions are the most characteristic and that subsequent lesions may be altered by metabolic or other factors. Osteoporosis due to senility or other causes and existing prior to metastasis may also alter the Roentgen picture. Radiotherapy may affect the pathologic picture by producing fibrosis. The work thus far is by no means conclusive and numerous factors remain to be investigated.

The Clinical Value of Roentgen Measurements of Heart Size.—It is admitted by HODGES (*Radiology*, 1933, 20, 161) that Roentgen studies of the heart have not, in the past, been regarded by cardiologists as of any considerable value. To be sure, calcification of the pericardium, aneurysm of the aorta and gross enlargement of the heart have long been recognizable roentgenologically, but casual reports by the roentgenologist of an "aortic heart" or "mitral heart" have not greatly impressed the cardiologist. If, however, roentgenologists will report exact areas and transverse diameters under standard conditions, including heart rate at the moment of examination and perhaps arterial and venous blood pressure readings; if they will accompany their report with a true sized diagram of the heart in relation to normal landmarks, and will compare the measurements thus obtained with predicted normal measurements for the individual patient, their efforts must soon be rewarded by the clinician's recognition of the real value of such assistance. Accurate methods of making such measurements are readily available and there seems to be little reason for attempting interpretation without employing them.

Bilateral Diaphragmatic Hernia.—MAY (*Radiology*, 1933, 20, 275) reports a case of bilateral diaphragmatic hernia in a woman aged 60. The patient had passed 3 examinations for life insurance and had no symptoms suggestive of hernia until after an operation for a huge uterine fibromyoma. On roentgenoscopic examination with an opaque meal the barium was seen to descend into the cardiac end of the stomach, ascend into the corpus above the diaphragm and then descend again to the pylorus below the diaphragm. After 6 hours the barium had reached the middle of the transverse colon. The visualized ascending colon protruded into the thorax through an aperture at the right sternocostal attachment of the diaphragm. In the chest this part of the colon formed a loop around the stomach and then reentered the abdominal cavity. Operation was refused by the patient.

NEUROLOGY AND PSYCHIATRY

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Traumatic Parkinsonism.—CONSO (*Thèse de Paris*, 1932, p. 159) records an illustrative case in a man, aged 32 years, following a fall off a bicycle. He maintains that Parkinsonism of traumatic origin undoubtedly does exist, although in a number of cases the trauma is merely a coincidence and there is another cause of the encephalitis, while in others trauma has merely acted as an exciting cause, as in some

cases of general paralysis. Anatomically there are some rare cases on record in which circumscribed lesions of the nuclei of the base of the brain have been found to account for the existence of a traumatic Parkinsonian syndrome. Clinically, the syndrome is differentiated from paralysis agitans by the constant presence of the tremor, which is sometimes very localized, the early appearance and progressive character of plastic contractures, and the intensity of subjective pain of a thalamic type. Moreover, the presence of pyramidal signs, the great frequency of psychic symptoms, especially depression, the absence of changes in the cerebrospinal fluid and the slowly progressive evolution of the syndrome are characteristic.

PATHOLOGY AND BACTERIOLOGY

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Multiple Liver Abscesses Caused by a *Leptothrix*.—A report of a case of leptothricosis with the formation of liver abscesses is made by HARRIS (*Am. J. Path.*, 1933, 9, 71). A short review of the literature reveals 2 cases of leptothricosis of liver secondary to gastrointestinal infection. The patient was a child, aged 11 years, who was admitted with weakness, fever, pain near right costal margin, abdominal distention and cough. Roentgen ray showed abscess of the right lung. Peritoneal fluid was sterile and contained red blood cells and lymphocytes. The patient died about 10 weeks after the onset of symptoms. Autopsy revealed an enlarged liver with adhesions to spleen, stomach, omentum and diaphragm. Section showed multiple abscesses throughout liver and in association with the bile ducts, filled with smooth yellowish-gray mucoid pus. One abscess had ruptured through the diaphragm causing a right pleuritis and lung abscess. Another extended to the pericardium, producing a purulent pericarditis. Microscopically the liver showed congestion, small hemorrhages and necrosis of cells, with infiltration of tissue by inflammatory cells. The abscess contained filamentous and bacillary forms of the organism. In the lung there was thickening of the pleura with inflammatory cells in the tissue and the bronchioles. *Leptothrix* was demonstrated in the bronchioles, alveoli and pericardial fluid. The organism was cultured with difficulty on yeast broth containing fresh tissue or pus, under anaërobic conditions. Abscesses were produced in guinea pigs and rabbits by subcutaneous inoculation of cultures. The source of the organism and the portal of entry are obscure. No lesion could be found in the gastrointestinal tract at autopsy although the possibility of a healed lesion was presented.

Cellular Inclusions in Cerebral Lesions of Lethargic Encephalitis.—Diseases caused by filterable viruses are characterized by cytological changes, which may be in the form of inclusion bodies within the cytoplasm or nucleus, hyperplasia of cells, or necrosis of cells. DAWSON (*Am. J. Path.*, 1933, 9, 7) presents a case of human encephalitis showing definite intranuclear inclusion bodies. The patient was a male, aged 16 years, admitted to hospital with rigidity and tremor, slow deliberate speech and masklike face, the condition becoming progressively worse with rise in temperature to 106° F., death resulting in 6 weeks. At autopsy the brain substance showed diffuse congestion and some edema but no definite areas of hemorrhage or necrosis. Sections through cerebral structures, cerebellum and spinal cord show two types of lesions: (1) Associated with bloodvessels showing congestion, hemorrhage and lymphatic infiltration of the adventitia. (2) In the individual cells, chiefly large ganglion cells and also neuroglial cells, are eosinophilic intranuclear bodies, which may be simple degeneration or necrosis, or phagocytosis. The bodies vary in size, number and staining properties and are separate from the nucleolus. They resemble morphologically the inclusion bodies found in herpes simplex, zona, varicella and virus III disease in rabbits, with several slight differences, and it is therefore suggested that in this case a filterable virus may have been associated with the lesions. Two other cases of clinical encephalitis lethargica are reported in which the vascular lesions of the central nervous system were present, but the inclusion bodies were not demonstrable. These findings suggest that encephalitis lethargica may not be a clinical or pathologic entity, but an ill-defined group, of varied etiology and manifestations. Animal inoculation of emulsions from all 3 cases failed to produce any demonstrable infection.

A Comparative Study of Subcutaneous Nodules in Rheumatic Fever and Rheumatoid Arthritis.—DAWSON (*J. Exp. Med.*, 1933, 57, 845) collected a series of cases of subcutaneous nodules in rheumatic fever and rheumatoid arthritis. He compares the two with regard to frequency, situation, size, duration, type of case, etc. Furthermore he discusses the detailed microscopic pictures in these two types of nodules. He concludes that although subcutaneous nodules in rheumatoid arthritis and rheumatic fever are not necessarily specific for these two diseases, yet when found in cases of either disease they are identical and represent different phases of the same fundamental pathologic process. This lends further support to previous conceptions that rheumatoid arthritis and rheumatic fever have a common etiology, and are different only in the type of response of the affected individual.

Experimental Nephritis Produced by the Styryl Quinolin Compound No. 90.—SHEEHAN (*J. Path. and Bacteriol.*, 1932, 35, 589) has produced an acute nephritis in rabbits by injection of a styryl quinolin compound, No. 90. The nephritis results from a single dose and is characterized by necrosis of the whole first convoluted and spiral tubule and a severe degeneration of the broad ascending limb of Henle. Regeneration of the tubular epithelium follows with the subsequent development of fibrosis about the regenerated tubules which gradually atrophy and disappear. The associated glomeruli remain intact for about 6 months

and then also atrophy. The severity of the nephritis is gauged by the rapidity of the initial rise of the blood urea. In animals which survive a moderately severe nephritis for over 2 months the blood urea shows a slight permanent rise while the concentrating power becomes normal. After a harmless dose of No. 90 the epithelium of the first convoluted tubules removes the dye directly from the blood stream, the absorption depending on the physiologic activity of these tubule cells and is inhibited by their previous damage. It is believed about half the dye taken up at the beginning by the tubule cells is secreted into the lumen of the tubules within the following 24 hours, while the remainder disappears, possibly due to intracellular destruction. Following a nephrotoxic dose, a similar absorption and excretion occurs, but the cells are damaged by accumulation in their cytoplasm of large amount of the dye. This initial damage is probably completed by the retention of the dye in the cells, owing to the diminished urinary excretion in proportion to the extent of the lesions.

Primary Carcinoma of the Liver.—In a total of 17,664 autopsies conducted in the Tan Tock Seng Hospital, Singapore, TULL (*J. Path. and Bacteriol.*, 1932, 35, 557) found 134 cases of primary carcinoma, giving a percentage of 0.76. Of these, 126 occurred in Chinese, who form 83 per cent of the Hospital's patients. The ages varied from 28 to 76, the great majority being almost evenly distributed through the fourth, fifth and sixth decades. The patients were nearly all of the coolie class. Symptoms were of short duration, no patient surviving their onset more than 3 months. Ascites occurred in 63, jaundice in 46. Only 12 complained of pain, which was never severe. A tumor was palpable in 91 cases, edema of the legs was seen in 112, while distention of the superficial abdominal veins was observed in 70 cases. Flukes were not commonly present. Splenomegaly occurred in 52. The liver was definitely enlarged in 126 cases and showed a constant distortion. The right lobe is much more frequently involved than the left (69 to 11), while the gall bladder is seldom affected. Cirrhosis was present macroscopically in 98 cases. The gross appearance of the liver is characteristic, showing (a) a single spherical mass; (b) discrete, nodular masses throughout; or (c) diffuse growth through entire organ. In spite of very extensive involvement, the liver may function normally. Ninety-nine cases were of the liver cell or hepatoma type, while 35 were of the bile duct or cholangioma type. The hepatoma is distinguished by a greater variety of cells, no acinar formation and a fine capillary stroma as a constant feature. Metastases are less frequent than in primary carcinomata of other organs, being found in the diaphragm in 32 cases, lungs in 31, and abdominal lymph glands in 24 cases.

Causes of Cell Death in Irradiated Human Tissue.—Although many theories have been advanced to explain the destructive action of radium and Roentgen rays, most authors assume that the rays destroy cancerous growths wholly or in part by virtue of a direct selective action upon the malignant cells. PULLINGER (*J. Path. and Bacteriol.*, 1932, 35, 527) supports a theory of indirect action through lesions in bloodvessels based upon a study of 87 surgical and 83 postmortem specimens of human tissue irradiated with radium and Roentgen ray for various

types of malignancy. The author's observations were confirmed by surface irradiation on healthy rabbits. A regular series of events occurs in bloodvessels following irradiation, the earliest being an extreme degree of vasodilatation affecting chiefly thin-walled, loosely supported capillaries and veins and may be followed by stasis of blood and local edema. The engorged vessels may next become the site of small platelet thrombi, due probably to mechanical damage to endothelium. This thrombosis may extend, producing necrobiosis or infarction. The picture of engorged, thrombosed vessels without bacterial inflammation is stated to be extremely characteristic of recently irradiated tissues. Endothelial injury may also lead to exudation of serum or extravasation of blood. The consequence of any of these events is cell death, produced slowly by necrobiosis or more rapidly by coagulation necrosis. Healing begins early, with abundant proliferation of capillaries and fibroblasts. The resulting fibrosis leads to further cell death from pressure atrophy. A favorable end result is an extremely hard, acellular, non-vascular scar. The apparently selective action upon new growths can be accounted for by the fact that tumors are supplied by ill-formed capillaries loosely supported by tumor cells with deficient collateral circulation.

HYGIENE AND PUBLIC HEALTH

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Acute Endemic Upper Respiratory Diseases.—DOULL (*Canad. Pub. Health J.*, 1930, 21, 105) summarizes our knowledge of acute upper respiratory diseases. He states that there is an apparent synchronism in peaks of respiratory disease, not only as between different groups in the same area, but in various parts of the United States. A similar finding has been reported from Holland. Certain upper respiratory conditions, classed as "common colds," may be transferred to healthy human beings by means of filtered nasopharyngeal secretions of early cases. Likewise, a similar acute condition has been transferred from man to ape. Intensive bacteriologic studies have failed to demonstrate constant and positive association of any microorganism with acute upper respiratory disease, save in acute follicular tonsillitis. No method of prophylaxis has been demonstrated to be of value. LONG, BLISS and CARPENTER (*Bull. Johns Hopkins Hosp.*, 1932, 51, 278) believe it possible that at times the common cold is transmissible during the incubation period. According to GAFAFER (*J. Infect. Dis.*, 1932, 51, 489), those with tonsils and adenoids and those without tonsils and

adenoids present no significant difference with respect to frequency, severity or type of attack of disease of the upper respiratory tract (common cold). PALMER (*Am. J. Hyg.*, 1932, 16, 224) found no evidence of association between size of frontal sinus and the number and duration of attacks. GAFAFER (*Am. J. Hyg.*, 1932, 16, 880), who studied groups with brown eyes and with blue eyes found no significant difference in respect to frequency, severity or type of attack of upper respiratory disease. The same investigator (*Human Biol.*, 1932, 4, 429) observed Jews and non-Jews and reports like findings in these groups.

Lethal Effect of Alternating Current on Yeast Cells.—TRACY (*J. Bacteriol.*, 1932, 24, 423) determined quantitatively lethal temperatures for a strain of *Saccharomyces ellipsoideus* in grapejuice for 1, 5 and 15 minutes. By passage of alternating current through yeast cell suspensions in grapejuice at non-lethal temperature, 42° C., pronounced killing effects were obtained, indicating that alternating current of 60 cycles exerted a lethal action independent of temperatures. The lethal effect of the current varied with the current density and quantity of electricity used. Electrically treated grapejuices, after prolonged exposures of 30 minutes, were not toxic nor lacking in nutrient values for yeast. The gases evolved from electrolysis were not toxic to yeast cells. It is possible that the killing effect exerted by alternating current on yeast cells is caused by the formation of temporary toxic substances like free chlorin, and that these are immediately reduced upon cessation of the current, and thus disappear. Such an action as this would directly follow the electrical conditions determined as necessary for killing the yeast cells.

The Rabicidal Antibody Content of Rabbit Immune Serum as an Index of Acquired Resistance to Rabies Infection.—STUART and KRIKORIAN (*J. Hyg.*, 1932, 32, 489) state that a practically identical degree of anti-rabies immunity can be secured by the exhibition of equal quantities by weight of etherized virus, fresh-fixed virus or carbolyzed virus over equal periods of time. Although, in general, some indication of anti-rabies immunity is afforded in treated rabbits by the rabicidal antibody content of their blood, no mathematical relationship can be established.

Protective Value for Infants of Various Types of Vitamin D Fortified Milk.—MITCHELL *et al.* (*Am. J. Pub. Health*, 1932, 22, 1220) again emphasize the discrepancy between the rat assays of antirachitic agents and the protective and curative value of such agents for human infants. Three types of vitamin D fortified milk were studied; namely (a) irradiated pasteurized milk; (b) "yeast milk," and (c) milk from irradiated cows. Parallel studies were conducted on rats with all 3 types, and studies on infants with the first and third types. Some curative studies, however, were made upon infants with "yeast milk," the second type. The amount of vitamin D by assay and the protection afforded infants against rickets by the first 2 types were found to be equivalent in most respects to the favorable results reported by other investigators. Preliminary investigations of milk from irradiated cows, both by rat assay and by protective and curative experiments on human infants, would

suggest a definite increase in vitamin D potency over the milk from control cows. Twenty infants over a period of 6 to 8 months were protected from rickets by this antirachitic agent alone. One infant in the foundling home and a small number of other infants with definite rickets were cured by this same agent alone. These data are not regarded as conclusive until the group of infants has been followed for a longer period. The rat assay on milk from irradiated cows approximated 22 units of vitamin D per quart of milk. The apparent effectiveness in preventing rickets in infants by such a small number of vitamin D units emphasizes the importance of certain unknown and unmeasured factors in vitamin D fortified milk which deserve further consideration and study.

Subcutaneous and Intradermal Smallpox Vaccination.—ROBERTS (*J. Prev. Med.*, 1932, 6, 453) discusses the use of the subcutaneous and intradermal methods of vaccination over a period of 4 years among 266 children in an institution. A simple technique which could readily be adopted in ordinary practice. The best results in the work at this institution were obtained by the intradermal method, using living virus in dilutions of around 1 to 1000. The reactions were mild, and vesiculation and scarring were trivial or absent. The appearance of vesicles and scars was even less frequent following subcutaneous vaccination with high dilutions, but persistent indurations were occasionally an undesirable result of this method. It is possible that this was due to the comparatively large dosage (1 cc.) and that further studies, using smaller dosage, might be of value. Subsequent revaccination, sometimes performed as long as 4 years after the initial vaccination, revealed no appreciable difference in the degree of immunity conferred, as compared with the cutaneous method, irrespective of the dilution. The advantages of the subcutaneous and intradermal methods outweigh the disadvantages and their wider use is recommended.

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THE
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DIABETES MELLITUS—PROBLEMS OF PRESENT-DAY
TREATMENT.*

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At the present time about 2000 diabetes deaths are registered annually in New York City, and the diabetes death rate is about 50 per cent higher than it was only 20 years ago. Approximately the same condition exists in all the large cities of the United States and more or less throughout the civilized world. A brief analysis of these facts, and possible remedial measures for them, are given in this paper.

Statistics. Chart I shows that for persons of both sexes the diabetes death rate in New York City has risen from 2.2 per 100,000 of population in 1871, to 29.3 in 1932. The total number of deaths has risen from 25 in 1871, to 2116 in 1932. A distinct rise in the number of diabetes deaths is registered not only in New York City but throughout the United States, as shown by the mortality statistics from other cities.

The death rate for males and for females was almost the same up to 1905, but thereafter the rates for the two sexes diverge—that for females rising more sharply, so that by 1932 the rate for females

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was about double that for males. The same change in trend about 1900 is noted in the individual age groups, as will be shown subsequently.

It should be understood that the term "diabetes death rate" is really only a record of persons who have had diabetes mellitus and is not a true indication of the deaths actually caused by that disease. In a sense, it reflects the incidence of diabetes. Diabetes is usually, though not always, given preference as the cause of death which is officially recorded when more than one condition is mentioned on the death certificate.

CHART I.

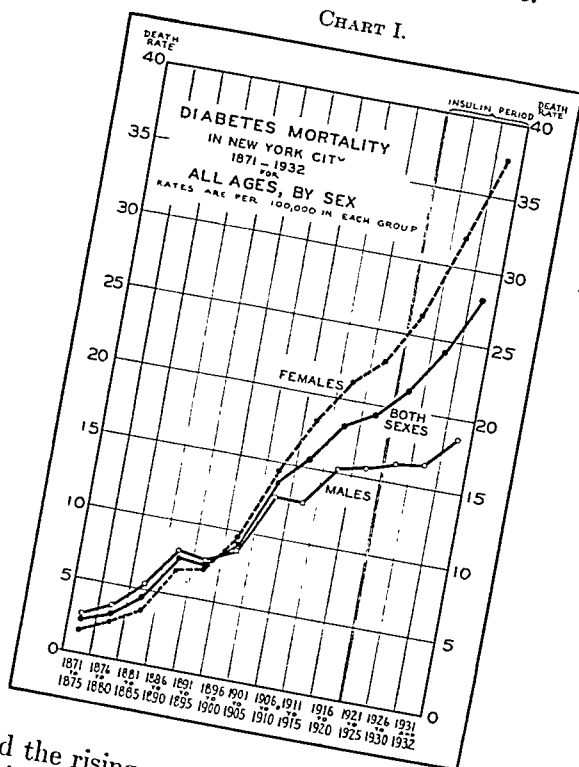
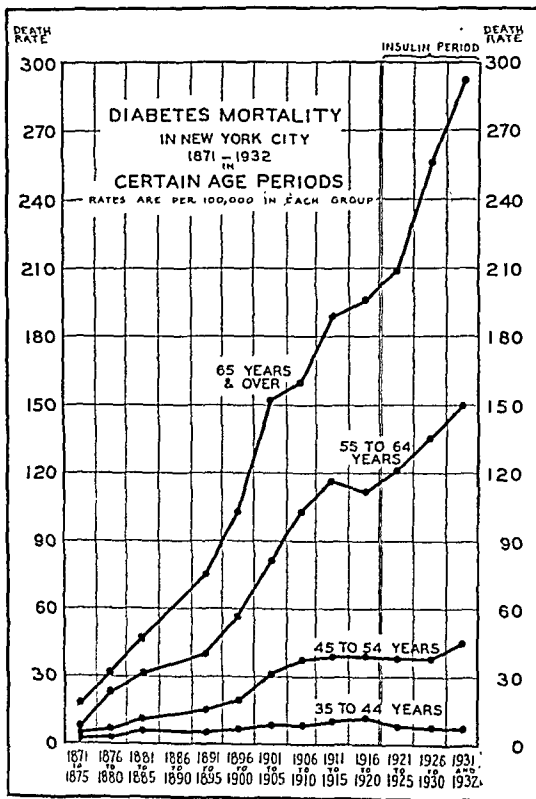


Chart II, and the rising scale for the death rate in the graphs of Chart III, furnish ample evidence of the increasing prevalence of diabetes in the older age periods. There are certain additional facts to be deduced from Charts II and III. A change in the trend of the mortality rate occurs in nearly all age groups about 1900. The most probable explanation of this fact is the introduction of the international classification of the causes of death by the Department of Health of New York City in 1901; this system of recording deaths has been followed from that time on, and consequently the statistics in regard to New York City are only strictly comparable from year to year since 1901.

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E. Rogers

We have presented the mortality statistics for New York City from 1870 to 1932 but warn against any reliance whatever being placed on the statistics prior to 1901. Diabetes was formerly regarded as a rare disease, but our study has convinced us that this was largely due to the inaccuracy and the rarity of urine examinations a few decades ago. Prior to about 1850, the presence of sugar in the urine was usually detected only by taste, or by sugar crystals obtained by evaporating the urine. Trommer's test was first described in 1841, and Fehling's test in 1848. A study of the medical histories of so efficient an institution as the New York

CHART II.

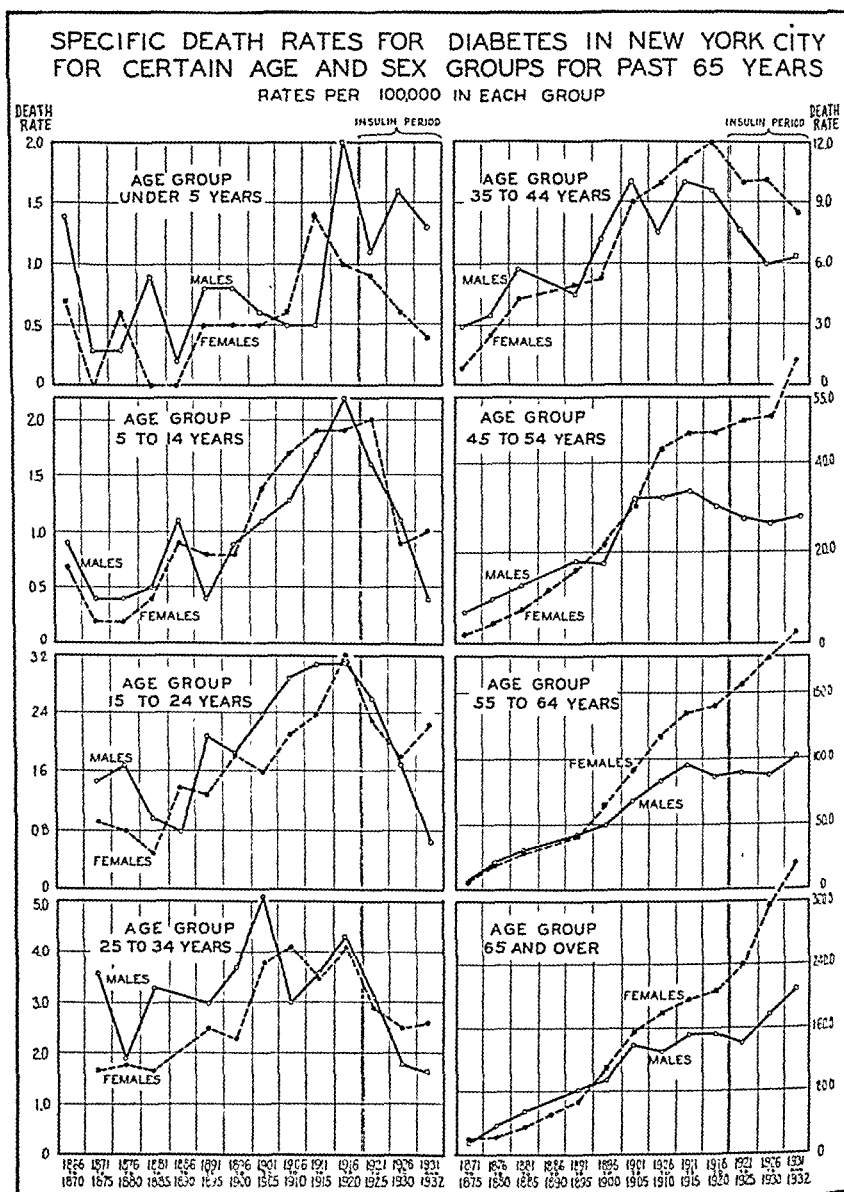


Hospital shows that, during the '60's, '70's and '80's, routine urinary examinations for sugar were not made. It is clear that in the practice of private physicians such tests were even less frequent. In other words, diabetes was usually not detected. Evidently the rise in the registered mortality of diabetes during more recent years is due, to a very great extent, to the acceptance of urine analyses as a routine part of physical examinations.

After 1920 there is a marked improvement in the death rate in females under 45 and in males under 65 years of age (Chart III). This may be definitely attributed to the effective use of insulin. In women over 45 years (Chart III) the rise in the death rate con-

tinues its previous upward trend in spite of insulin, while in men this is true only in the age group of 65 years and over. This increase

CHART III.



in diabetes deaths of older females is so great that it outweighs the favorable influence of insulin in the other age and sex groups and results in a distinct rise of the diabetes mortality as a whole.

It is true that physical examinations are more frequent and more thorough than they were a few years ago. This produces an apparent rise of the diabetes mortality rate. The data concerning this disease, obtained from 24 hospitals in New York City for the year 1931 by Dr. Alice Paulsen, shows that much remains to be accomplished in this direction; of 1617 cases of diabetes treated in these institutions, 318 (19 per cent) were diagnosed only after admission to the wards for the treatment of some other ailment. The greatly increased number of applications for life insurance by women and their more frequent participation in business activities, both entailing medical examinations, undoubtedly are factors which add to the recorded prevalence of diabetes in this sex during recent years. Inquiry of several large life insurance companies shows that the percentage of women among those examined for life insurance in the so-called "ordinary" business (with medical examinations including urine tests) has about trebled in the past 30 years and women policyholders now constitute a considerable proportion of the whole.

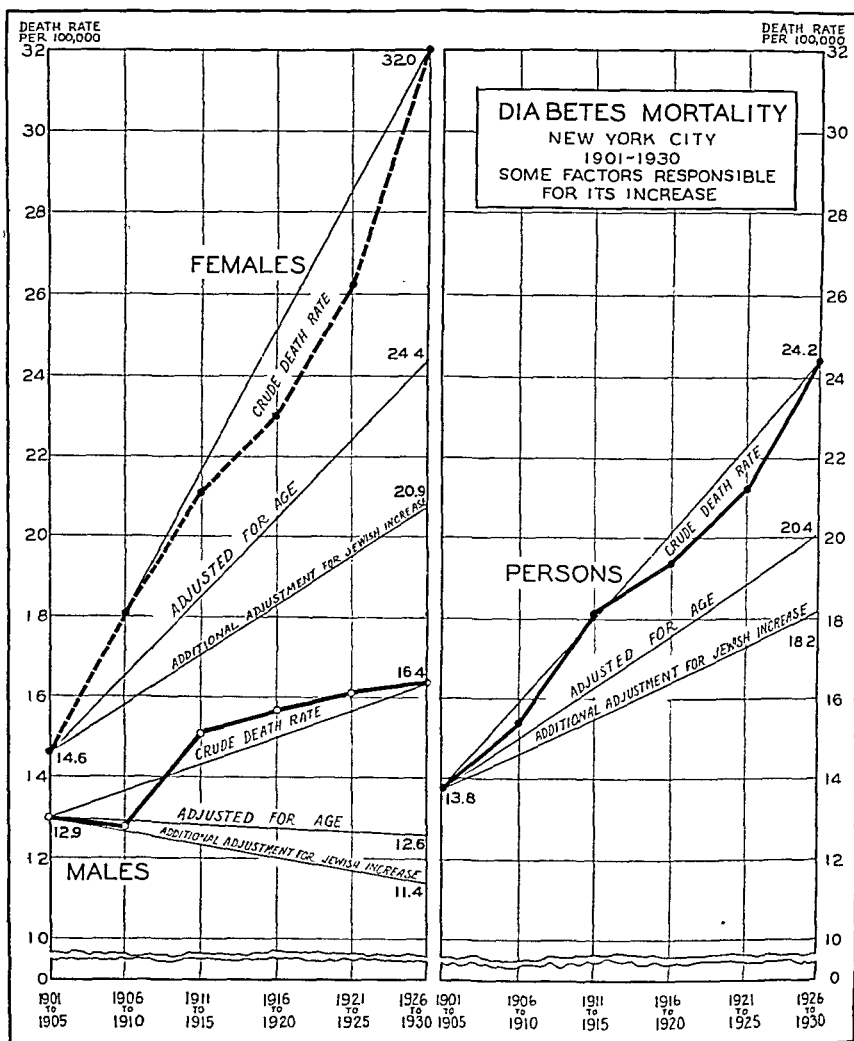
There has been a distinct aging of the residents in New York City. The age group 45 to 64 years was 13.1 per cent of the entire population in 1900, while in 1930 it constituted 17.3 per cent; in other words, the proportion of persons aged 45 to 64 years increased over 32 per cent during the last 30 years. Similarly, the age group 65 years and over changed from 2.8 per cent in 1900 to 3.8 per cent in 1930; an increase of more than 35 per cent. These facts have a distinct bearing on the interpretation of the mortality statistics. Drolet¹ computes that in the light of these figures the diabetic death rate for New York City in the 30 years from 1900 to 1930 rose only 58 per cent, whereas according to the crude death rate not adjusted to the aging of the population or the growth of New York City, the increment was nearly 100 per cent.

The large Jewish immigration during 1900 to 1915 is still another fact which should be considered in accounting for the rising mortality rate of diabetes in New York City. The proportion of Jews in the city's population has nearly doubled since 1900. A study of the statistics for 1931 shows that the diabetes mortality is 75 per cent higher among Jews than non-Jews.² The increase in the Jewish population has therefore been an important factor in raising the city's diabetes mortality rate.

The calculated diabetes death rate in New York City for 1930, allowing for changes in the composition of the population with respect to the age distribution and the proportion of Jews since 1900, is shown in Chart IV. The elevation of the total diabetes mortality during 30 years is only from 13.8 to 18.2, instead of 24.4 per 100,000. This reduces the rise calling for explanation during these thirty years from 76.8 to 31.9 per cent. It is noteworthy, when the appropriate corrections are made for the composition

of the population in regard to age and proportion of Jews, that the diabetes death rate for males actually indicates a decrease since 1900 (Chart IV). For males at least, diabetes in New York City has not been growing more prevalent. In females the figures, corrected as for males, show an elevation of the death rate from

CHART IV.



14.6 to 20.9 per 100,000 between 1900 and 1930, an increase of 43.1 per cent (Chart IV). This points to some distinct difference in the susceptibility to diabetes in the two sexes. This may be partly explained, as previously mentioned, by the growing participation of women in industrial affairs and their subscribing to life

insurance, both of which entail physical examinations. Other factors affecting the two sexes differently will be taken up subsequently.

While these statistical facts lessen the significance which should be attached to the rise in the registered mortality of diabetes, they in no way lessen the great importance of diabetes as a health problem.

The use of insulin has effected great changes in the clinical course of diabetes. According to Dublin's statistics (data of Dr. E. P. Joslin analyzed by the Metropolitan Life Insurance Company) there is a drop from 1900 to 1930 of about 50 per cent in the diabetes deaths due to coma. There is a rise of about 35 per cent in those attributed to cardiovascular conditions, renal disease and gangrene, and of about 15 per cent in diabetic deaths from all other causes.

It is certain that Joslin's results are probably more favorable than those of any other clinic, but even they do not achieve the ideal of perfect control, that is, the entire elimination of diabetic coma. The carelessness of patients and the disregard of diabetes during surgical and other emergencies are mainly responsible for the persistence of a considerable number of coma deaths. The increasing frequency of arteriosclerosis and its complications in the diabetics who live to grow old, thanks to insulin, is well shown in these figures. In our experience the diabetic who has maintained a sugar-free urine almost constantly will not develop these much-dreaded complications. However, the determination of exactly which factors are concerned in the causation of arterial changes and their sequelæ is one of the most urgent problems in our effort to check diabetes. Only when this subject is completely elucidated will it be possible to state with assurance, what can now be only tentatively claimed, namely, that the complete and constant control of diabetes virtually amounts to a cure, even if the disease itself cannot be eradicated.

Treatment. The principles of the treatment of diabetes are established on as sound a basis as is possible with the present-day knowledge of normal and pathologic carbohydrate metabolism in human beings. The accepted criteria for successful treatment are: the constant maintenance of normal nutrition, blood sugar and plasma cholesterol, and a urine free from sugar in the clinical sense. These are very high standards, for it is debatable whether or not the unwavering adherence to natural levels of blood glucose and cholesterol is very significant. The remedial measures, however, used to achieve these ideal objectives of therapy, leave much to be desired.

Within the short period of one generation clinicians have participated in controversies concerning the exclusive administration to diabetics of diets that were, physiologically speaking, distinctly bizarre. We refer to the starvation and high-fat systems of feeding and to the more recent advocacy of excessively large amounts of starch. While extreme diets of this sort meet certain emergencies,

they cannot be used continuously without grave consequences. The routine food intake of the diabetic must be considered suitable in the measure in which it meets the vital needs and the personal tastes of the patient.

Radical changes in the diet may be required for many reasons, such as excessive loss or gain in weight, variations in the carbohydrate tolerance, shifting in the level of the blood sugar and cholesterol, an aversion to or a strong desire for certain foods, the demands incident to surgical intervention or infectious diseases. Essential alterations in the diet should be made only after thoughtful study; carried out by the patient without the aid of medical advice they entail an unwarranted responsibility. For this, as well as for the other reasons to be mentioned subsequently, more frequent medical counsel and less self-treatment than is advocated in many quarters seem desirable in the routine care of diabetic patients.

Many physicians, nurses and patients are openly scornful of the use of qualitative as opposed to quantitative, *i. e.*, weighed diets. Patients with this point of view can be accommodated without distressing or inconveniencing any one except themselves; but the physicians and nurses who insist on accurately weighed and meticulously calculated diets for all cases may spread discontent, and tend to impose an unnecessary burden on many already afflicted with a permanent handicap. Weighed diets are undoubtedly necessary for the satisfactory control of many cases of diabetes, but eating by grams should be avoided whenever possible, since the attendant ceremony and formality tend to provoke an undue nervous tension. A rational dietary, without sugar or sweets, in which the amounts of food with a high-carbohydrate content are approximated by household measures, may often be advisedly carried out when the patient is using insulin. But again, the responsibility should rest entirely with the physician who should be the arbiter of what is most advantageous in each case.

Finally, as regards the self-regulation of the diabetic patient, this disease when it has once appeared is a lifelong problem and its treatment, if it is allowed to become a fulltime occupation to the patient, tends to prove irksome and to result in nervous strain that affects the carbohydrate tolerance unfavorably. The daily urine analysis of a 24-hour specimen by the patient is not advisable. In the first place, the analysis of several single specimens usually yields more valuable information for the regulation of treatment, since this method of examination will determine in which meal the carbohydrates are in excess, or which dose of insulin is insufficient; in the second place, the collection of a complete 24-hour specimen is usually accomplished only with some discomfort and sacrifice; in the third place, the analysis of the patient's urine by himself or one of his family, is likely to be associated with considerable introspective doubt.

Taking all these facts into consideration, it is suggested that the amount of responsibility for self-examination and treatment should be reviewed for each patient with great care. Some patients are unable to be objective about their condition and are rendered unhappy by self-investigation and regulation, while others are able to examine their urine and conduct their treatment very effectively without detriment to themselves.

The family physician should be the hub of the wheel about which routine management of the diabetic patient centers. Postgraduate medical instruction in the simple, direct, effective treatment of diabetes should be constantly available in every large city and thus make it possible for every practitioner to review the principles and methods of therapy at all times. Every hospital should have its resources so organized that the medical, surgical and nursing staffs, the laboratories and diet kitchen are capable of meeting all diabetic problems and emergencies. The occurrence of coma, of a severe infectious disease or other complication in a diabetic patient may call for almost hourly observation and therapeutic adjustment, and is therefore much more satisfactorily controlled in a properly equipped institution than by a single physician in the patient's home. While the routine treatment of the diabetic should be carried out by the family physician, additional medical advice should be sought by him when the ideal objectives of treatment are not maintained, since a deviation from them for a few years or even a few months will result in irreparable damage.

Etiology. The cause of diabetes must be thoroughly understood if reasonable and effective measures are to be carried out for its prevention and cure. The diagnostic criteria and the causes of diabetes have not been satisfactorily defined and, consequently, not all the steps intended to control this disease can be advocated with complete confidence. The enforcement of guides to health, whose validity is not fully established, may result in harm as well as good. We are convinced that all the factors concerned in the causation of diabetes should be subjected to thorough scrutiny and further study, and that meantime public health education on diabetes be confined to an organized effort for the broadcasting of the known facts in regard to the prevalence of diabetes, and the necessity of the conscientious and continuous enforcement of the principles of treatment.

Definition and Diagnosis. Diabetes mellitus may be defined as a disturbance consequent upon a diminished ability of the body to utilize glucose. This is very brief and simple and certainly correct as far as it goes, but it is open to criticism since it does not include the cause of the disease. The impairment of carbohydrate tolerance is usually attributed to changes in the pancreas. Postmortem examinations often reveal such lesions but there are so many instances in which the pathologist fails to demonstrate adequate abnormality

that some skepticism concerning the validity of the unitarian doctrine of the pancreatic etiology of diabetes is justified. The activities of many glands besides the pancreas, such as the adrenal, the thyroid, the liver, the pituitary and numerous others, some partially explored, others scarcely thought of, play a rôle in the assimilation and the oxidation of glucose. The fact that insulin remedies the situation does not warrant our regarding this as a purely substitutional therapy for pancreatic deficiency because its effects may be in part compensatory for an altered activity of other glands. We must consider, therefore, a diminished tolerance for glucose which, according to some is invariably due to pancreatic disease, but, according to others, to extrapancreatic disturbances as well.

The fact that diabetes is thought of primarily as a disease characterized by an impairment of carbohydrate tolerance is demonstrated by the nature of the only diagnostic measure for diabetes in common use today, known as the sugar, or glucose, or carbohydrate tolerance test. This test concerns itself solely with the ability of the body to utilize carbohydrates. Every case of diabetes exhibits a diminished glucose tolerance, but every instance of diminished glucose tolerance is not a case of diabetes. This shows that while our definition of diabetes is the best possible at the present time, it is not an exact description of the disease "diabetes" since there are no pathognomonic signs by which it can be identified. Improvement of the present-day treatment must be based on a clarification of these questions. The possibility that not one but several different forms of abnormal sugar digestion are included under the name "diabetes" is shown by the great and unexpected variations in its onset and in its clinical course.

Though diabetes cannot be accurately described, a consideration of the influences which favor its development is in order. The definition of diabetes is graphically presented in Chart V.

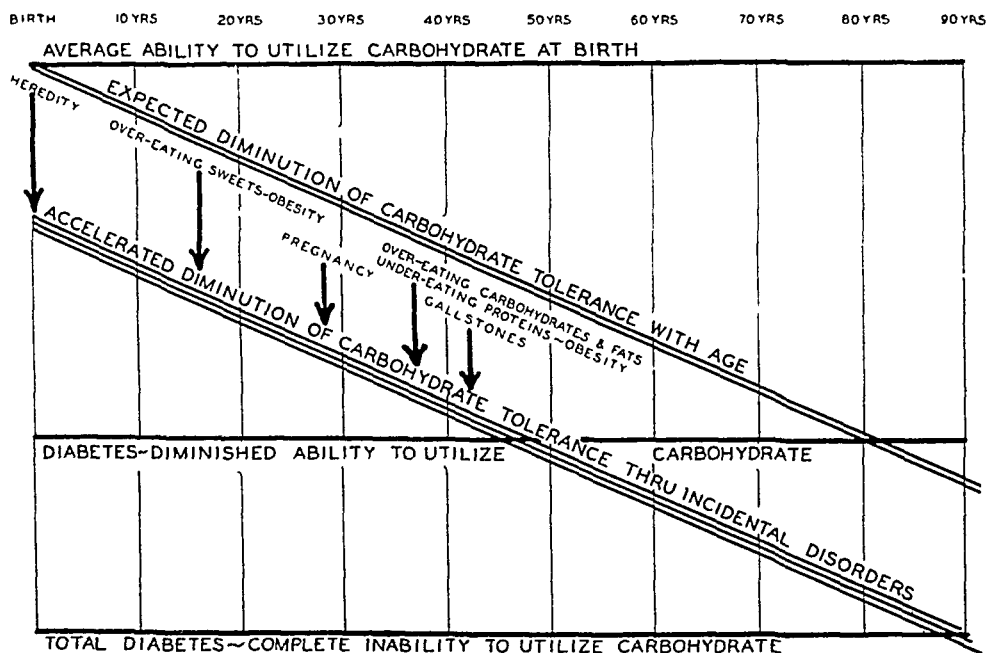
There are three horizontal lines indicating: first, normal carbohydrate tolerance; second, a degree of diminished carbohydrate tolerance at which point diabetes may be thought to begin; and third, the lowest line designed to represent the complete loss of carbohydrate tolerance which, when it exists in human beings, is called total diabetes. On these lines have been plotted the various influences that may in the course of a lifetime be expected to affect the carbohydrate tolerance.

Degenerative Processes, Arteriosclerosis. With advancing years degenerative processes manifest themselves in various organs and tissues in the body, including the glandular structures. This may be caused by the natural wear and tear of the tissues, or may result from arteriosclerosis. It accounts for the diminution of carbohydrate tolerance, that is the mild diabetes, of the aged. The falling line in Chart V, crossing the level of curtailment of carbohydrate tolerance indicative of diabetes at about 80 years of age, is a sug-

gestion of the average course of events in human existence. Some persons will give evidence of diabetes from this cause at 60, 50 or even 40 years of age.

Although this line is a purely arbitrary one, it is undeniable that a constant diminution of carbohydrate tolerance and a tendency to diabetes develops in practically all persons as the result of inevitable degenerative changes. We are accustomed to regard with equanimity rising blood pressure, thinning and graying of the hair, diminution of physical vigor and other marks of deterioration in older individuals, because they are considered to be the unescapable physiologic processes of the passing years. There is every reason to believe that the organs which control the metabolism of glucose

CHART V.—THE INHERENT TENDENCY TO DIABETES IN HUMAN BEINGS AND FACTORS THAT ACCENTUATE IT.



are affected in the same way. Thus the problem of the prevention of diabetes from this cause resolves itself into checking the diseases of old age, which is a general question for solution and is not to be specifically engaged in by those who are interested in perfecting means for the control of diabetes.

Heredity. Heredity is believed to be a factor in about 20 per cent of cases of diabetes. According to some careful investigation, heredity in diabetes appears to follow the Mendelian law. Insulin has enabled youthful diabetic patients to attain maturity and to become fathers and mothers, and has made it possible for the diabetic woman to carry through pregnancies successfully. Because diabetics, since the introduction of insulin, can have children in the

same proportion as normal persons, it is evident that the hereditary factor will result in a rising incidence of diabetes. The influence of an inherited diabetic tendency on the carbohydrate tolerance is indicated in Chart V. The degree and the rapidity of involvement of the carbohydrate tolerance indicated by the lines in Chart V will vary a great deal from case to case, and it must be understood that in its present form this graph expresses only tendencies, and not hard and fast curves of mathematical precision. The solution of controlling heredity as a cause for diabetes is, according to all present-day humanistic principles, not a direct one but a policy of patience that waits for the discovery of a cure for diabetes.

Pregnancy. Pregnancy has a marked influence upon carbohydrate tolerance and diabetes. Renal glycosuria, a permeability of the kidney to glucose below the normal level of blood sugar, is often found in pregnant women. This is a harmless anomaly, not a disturbance of the carbohydrate tolerance, and is not related to diabetes in any way. The consensus of experience is that during pregnancy diabetes may develop, that latent diabetes will be accentuated and that an existing diabetes will be aggravated. After pregnancy, carbohydrate tolerance may return to its antepartum efficiency or it may be permanently impaired. Pregnancy may therefore be considered as an immediate cause of diabetes in some instances.

Pregnancy may damage the carbohydrate tolerance but not to a sufficient degree to cause the immediate appearance of diabetes. The progressive diminution of carbohydrate tolerance expected with age would consequently reach the diabetic level at an earlier period of life in the woman who has borne children than in the one who has not. This idea is expressed in Chart V. This theory, which would be a large factor in accounting for the high incidence of diabetes in females over 45 years, could be either proved or disproved if comparative data were available of women who have borne children and of those who have not.

In this connection the following table showing the proportion of males and females among the diabetes deaths of single persons and those who were married or widowed is of interest.

TABLE 1.—DIABETES—DEATHS AND DEATH RATE IN OLDER ADULTS—NEW YORK CITY, 1931 AND 1932—BY CIVIL CONDITION AND SEX.

	Single.		Married and widowed.	
	M.	F.	M.	F.
Deaths in persons aged 45 years and over	126	106	1,095	2,392
Population in 1930, persons aged 45 years and over	82,494	82,450	644,285	643,827
Rate per 100,000	152.7	128.6	169.9	371.5

The marked preponderance of females among the deaths in married or widowed persons, in contrast to the relative proportion of males and females among the unmarried, lends support to the

belief that pregnancy is an important factor in determining the development of diabetes.

The relation of pregnancy to the diabetes problem, therefore, consists in the avoidance of strain or impairment of the carbohydrate tolerance during puerperium and childbirth. How this is to be accomplished is not known and it is a matter for further investigation to determine what can be done.

Gall Stones. Gall stones are often regarded as a cause of diabetes. A stoppage of the common duct by a calculus results in the forcing of bile into the pancreatic tissue and a consequent injury to the islands of Langerhans. In addition, cholecystitis will affect the carbohydrate tolerance adversely, as is the case with any infection, and it will accelerate degenerative processes and arteriosclerosis, thus favoring the development of diabetes. The interrelation between gall stones, diabetes, cholesterol metabolism, obesity and pregnancy is so complicated that it is impossible to explain it satisfactorily, and most phases of this problem are awaiting an intelligent solution. Since gall stones are more common in women of 40 years or over than in men, another factor besides pregnancy is indicated to explain the greater incidence of diabetes in females over 45 years of age.

The management of gall stones and their complications, with a view to effective prevention of damage to the carbohydrate tolerance, has thus far received scant attention and it would be futile to speculate on this matter because there is a lack of precise knowledge of this subject.

Diet—Obesity. Faulty habits of diet have been blamed for the increasing incidence of diabetes. Improper hygiene not only in regard to eating but also in other directions, especially sedentary habits and lack of exercise, has resulted in an increasing occurrence and degree of obesity which, according to the statistical evidence is associated with an excessive mortality rate in cardiac, arterial and renal diseases, in cancer and in diabetes. Overweight conditions should therefore be prevented if possible. Every degenerative disease gives evidence that obesity has a very adverse influence on the life of human beings. The underweight individual apparently has a better chance to live long than the so-called normal or ideal weight person. This really should be thought of as average weight of apparently healthy individuals, which implies something different than the term normal or ideal weight. The weight standards for the best health which are in vogue at present are apparently too high. Obesity evidently accelerates degenerative changes, that is, deterioration of the tissues and arteriosclerosis, which, as previously suggested, is one of the main processes concerned in the impairment of carbohydrate tolerance resulting in diabetes.

Nutrition is the difference between the amount of food consumed and the quantity utilized by physical effort. The storage of fat,

resulting in obesity, because of a lack of balance of these factors is not synonymous with overeating of fats, starches and sugars, though this is often taken for granted. Obesity is a condition that damages the tissues and strains the functioning organs. The first comes about through fatty infiltration of the tissues; the second is the result of the presence of an excess of body bulk which must be kept warm and which must be carried about. The two handicaps call for separate evaluation and different treatment in each individual. There is a distinct hazard for the obese subject if these two elements in the situation are not given individual consideration. Consequently, propaganda that is made concerning the dangers of obesity should be confined to the necessity and the means for the prevention of obesity, and the control of moderate gains in weight. The reduction of weight for the markedly obese individual, on the other hand, should always be carried out under medical supervision and should not be undertaken with the sole guidance of printed leaflets and radio talks.

The overeating of sugars, starches and fats will result in obesity. The high consumption of sugars and starches is often stated to be a cause of diabetes, independently of the effect they exert through the production of obesity. Charts demonstrating the parallelism between sugar consumption and the incidence of diabetes in different countries have been widely circularized. Such parallelism must not at once be interpreted as a relation of cause and effect. Recent studies in normal persons and in diabetic individuals show that the habitual eating of considerable quantities of sugars and starches improves rather than impairs the carbohydrate tolerance, provided glycosuria is not present. The conclusion, therefore, is warranted that the excessive use of starches and sugars favors the occurrence of diabetes indirectly through obesity, but that the consumption of starches and sugars, even in large amounts, is not a cause of diabetes. In fact, the available evidence indicates that it improves the sugar tolerance. Glycosurias, occurring after high-starch diets, point to a previously existing deficiency of carbohydrate tolerance, that is, a tendency to diabetes. According to these facts there is no reason for limiting the consumption of sugars and starches except insofar as these classes of foods will result in obesity.

The influence of obesity in some respects is more complex than it seemed when this subject was first studied. The association of overweight and hypertension has proved much less constant than originally supposed. Recent studies by Tyner³ show that "pre-diabetes" is equally associated with obesity and underweight, that the determining factor in the development of "prediabetes" is age, whose peak is reached in the seventh decade. The relation of obesity to diabetes, therefore, appears to be much more subtle than a simple, direct one of cause and effect.

The proportion of proteins, especially meats, in the average diet

is constantly diminishing. This implies that carbohydrates and fats replace the proteins and tend to cause obesity. Aside from this aspect, which has already been discussed, there is the danger that a deficient protein ration will result in tissue degeneration. Secondary anemia, edema and nephritis have been produced by such diets. It is very probable that an insufficient supply of animal proteins continued for a long time entails degeneration of various organs and arteriosclerosis, which will impair carbohydrate tolerance and accentuate any diabetic tendencies. An educational campaign for the proper use of animal proteins in the routine diet is urgently necessary.

Internal Secretions. The most significant factor in the control of diabetes lies in the functions of the glands of internal secretions. Except for the use of insulin, which has been discussed, there are no practical aids available for general application at present. Consequently, this important phase of the etiology of diabetes is omitted.

Summary and Conclusions. *Organization of Resources in Medicine.* Problems and questions without end have been touched on in this paper. For the promotion of their solution it is proposed that associations of metabolism clinics be organized in various cities. In New York such an association might well be under the auspices of the Academy of Medicine. The activities of such a section within the Academy should not be confined to diabetes, as there are too many other diseases to warrant the creation of a group solely for the study of diabetes, and by implication to segregate a certain number of physicians and specialists in diabetes. Many of us have believed for some time that applied physiology or functional pathology, or pathologic physiology, is as important as anatomic pathology for the understanding of this disease. The medical profession should recognize this by creating a younger brother of the pathologic society.* The phrase, "diseases of metabolism," is in common use but poorly defined; possibly it may be described as that group of disturbances depending upon functional pathology, such as diabetes, hypertension, and so forth. An association of metabolism clinics should bring about a very desirable unification and increased effectiveness of the present sporadic efforts in postgraduate teaching, gathering statistics, carrying out research, improving treatment and initiating preventive measures not only for diabetes mellitus but also for other diseases of equal, if not greater, importance from the point of view of public health.

The Incidence of Diabetes in New York City. Mortality statistics reflect the incidence of diabetes rather than diabetes as a cause of death. The use of insulin has prolonged the life expectancy of diabetic subjects so that, under ideal conditions of treatment, they

* As a pathologist I would like to point out that pathologic societies should, and generally do, regard pathologic physiology as much their field as pathologic anatomy.
—EDITOR.

should not succumb to diabetes but to the same diseases as persons not afflicted with diabetes. The method of registering the causes of death will have to be revised if a differentiation shall be made between the incidence and the true mortality rate of diabetes.

An adjustment of the diabetes mortality rate in New York City, according to the aging of the population and the influx of Jews for the past 30 years, shows that during this period the incidence of diabetes in males has not increased at all, while that in females has risen about 40 per cent. The more common and the growing incidence of diabetes in women may be ascribed to two factors: First, the greater participation by women in industrial activities and their more frequent subscription to life insurance, both of which entail physical examinations; second, the injurious effect of pregnancy upon the carbohydrate tolerance has a greater chance to manifest itself as diabetes now, compared to former years, because of our aging population. For these reasons we believe that the rising incidence of diabetes in New York City is more apparent than real.

Our statistics point to the fact that married women are about twice as likely to develop diabetes as married men, while there is no disproportionate ratio between the two sexes in unmarried persons; whether this may be the result of pregnancy directly, or indirectly, through the production of gall stones and obesity, or is due solely to obesity in married women, is an open question, though in our opinion, after a consideration of the available facts, it is pregnancy that impairs the carbohydrate tolerance which manifests itself as diabetes in many women after 45 years; the aging of the population and the use of insulin accentuate this effect of pregnancy on the diabetes mortality rate.

The prolongation of diabetic life through insulin enables men and women who are afflicted with diabetes to become fathers and mothers; consequently the hereditary factor should manifest itself in the future by a rise in the diabetes death rate.

Prevention of Diabetes. It is not feasible to accomplish a great deal in this direction until more complete and reliable information is obtained concerning the onset of diabetes at different ages and in the two sexes, and concerning the etiology of diabetes. The Department of Health can throw light on the problem of diabetes incidence by collecting the results of physical examinations from various sources and possibly by requesting reports of the discovery of diabetes by practitioners. The part played by heredity, menopause, pregnancy, gall stones, glandular activities, nervous disorders and other possible causes of diabetes calls for further investigation before popular statements can be finally and authoritatively made as to the influence these factors exert upon the carbohydrate tolerance in human beings. An educational campaign concerning the eating of meats, fats and carbohydrates, and the dangers of obesity is desirable and warranted by the available facts.

Diabetics Should Not Die of Diabetes. The methods and objectives of diabetes treatment available today are adequate to accomplish this. They are not as universally applied as they should be. In order to bring this about, the treatment should be simplified and be kept free from all unnecessary formalities; more responsibility should be assumed by the physician and less by the patient than is often advocated; opportunities for acquiring the facts concerning the routine management of diabetes should be always available for the practitioner of medicine in the larger cities; every hospital should have its resources so organized that the medical, the surgical and the nursing staffs, the laboratories and the diet kitchens are capable of meeting all diabetic problems and emergencies; every serious illness in a diabetic patient calls for hospitalization and not for home treatment; the physician should not hesitate about insisting on the constant maintenance of the ideal standards of treatment in all his cases, for a deviation from them within a few months or years will result in irreparable damage.

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THE FASTING BLOOD SUGAR IN SCHIZOPHRENIA.

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WITH THE TECHNICAL ASSISTANCE OF ELLA K. RUGGLES, S.B.*

For the past 5 years the Research Service of this hospital has been conducting an investigation on the schizophrenic psychosis. Among other objects of the research has been that of assembling data for a detailed description of the organic features of a representative group of patients with this psychosis. The details of the project have been previously reported.¹ This paper embodies a discussion of our findings regarding the fasting blood sugar.

The fasting blood-sugar levels in schizophrenia have been determined by a considerable number of investigators, but the results of the various studies have been by no means concordant. In general, as is shown in Table 1 (2 to 22), the results obtained have fallen into three categories. One group of observers has reported

* With the collaboration of the Research Staff of the Worcester State Hospital.

a fairly high incidence of hypoglycemia (below 80 mg. per 100 cc.) but with the majority of the subjects showing normal levels. In the six researches tabulated, 37 of a total of 156 patients (24 per cent) showed hypoglycemia. It is interesting that Smith and Hill⁴ found 8 out of 10 patients showed hypoglycemia but after 2 months' thyroid feeding all blood sugars were within normal range.

TABLE 1.—A. AUTHORS REPORTING INCIDENCE OF HYPOGLYCEMIA* IN MORE THAN 10 PER CENT OF PATIENTS.

	No. examined.	No. normal.	No. hypoglycemic.	No. hyperglycemic.
2 Genzel	13	10	3	0
3 Looney	40	33	7	0
4 Smith and Hill	10	2	8	0
5 Schrijver	31	22	6	3
6 Kasanin	33	26	5	2
7 Labin†	29	7	8	14
Total	156	100	37 (24%)	19

B. AUTHORS REPORTING HYPERGLYCEMIA‡ IN MORE THAN 10 PER CENT OF PATIENTS.

	No. examined.	No. normal.	No. hypoglycemic.	No. hyperglycemic.
7 Labin†	29	7	8	14
8 Heidema	13	3	0	10
9 Kooy	10	6	0	4
10 Wuth	40	25	0	15
11 Lorenz	52	39	0	13
12 Barrett and Serre	20	15	0	5
13 Mann	23	12	0	11
14 Joó	14	10	0	4
Total	201	117	8	76 (38%)

C. AUTHORS REPORTING HIGH INCIDENCE OF NORMAL FINDINGS.

	No. examined.	No. normal.	No. hypoglycemic.	No. hyperglycemic.
15 Newcomer	6	6	0	0
16 Henry and Mangann	9	9	0	0
17 McCowan and Quastel	29	29	0	0
18 Ström-Olsen	6	6	0	0
19 Weston	30	27	1	2
20 Raphael and Parsons	20	17	2	1
21 Bowman <i>et al.</i>	57	51	1	5
22 Sleeper and Hoskins	135	115	12	8
Total	292	260 (89%)	16	16
Grand totals	620	470	53	97
(Duplication eliminated)		76%	9%	15%

* Hypoglycemia = 79 mg. per 100 cc. or less.

† Labin appears in two lists.

‡ Hyperglycemia = 121 mg. or more.

A second group of studies made on 201 patients showed an incidence of hyperglycemia in 117 (58 per cent). Labin's 29 patients fall in this group as well as in the preceding.

Finally, records of 8 studies on a total of 292 patients showed

fasting blood-sugar levels within the normal range in all but 32 individuals. In this group, 89 per cent were normal. Newcomer,¹⁵ working with but 6 patients, examined weekly blood samples for from 4 to 7 weeks and found all values to lie within the normal range.

All told, then, we have reports of 620 patients, 76 per cent of whom showed a normal range of blood-sugar findings, 9 per cent showed hypoglycemia, and 15 per cent showed hyperglycemia.

A few other reports are available that do not lend themselves to tabulation. Pighini²³ stated that the blood sugar in schizophrenia is normal, but did not include the data upon which the generalization was based. Drury and Farran-Ridge²⁴ reported the average values of 18 patients whom they divided into four groups. In females in an acute phase of the psychosis the mean level was 130 mg. and in chronic cases 125 mg. In males the values were 118 and 115 mg., respectively. Reiter,²⁵ without giving quantitative details, stated that in his experience hyperglycemia occurred no more frequently in schizophrenic than in normal subjects. Tsuchiya²⁶ in 12 cases found a blood-sugar range from 65 to 100 mg., 3 findings being definitely within the hypoglycemic range. Uye-matsu and Soda²⁷ in 32 patients found a range from 77 to 142 mg., with an average of 99. Their subjects were all catatonics, and the samples were taken 2½ hours after breakfast, hence the results are not strictly comparable with those of the authors previously mentioned.

So far as can be judged by the reports, in none of the studies cited have the results been analyzed statistically with a view to showing any correlations that might exist between the blood-sugar levels and such variables as age, duration of psychosis, period of hospitalization, sex, or type of schizophrenia. Commonly even the emotional state of the patient at the time the sample was taken has not been reported.

Present Study. As previously noted¹ we have had available a group of patients who have served as subjects for an elaborate schedule of studies. Being tested has thus become their daily routine. In such a group, emotional reactions to the testing as such should produce the minimal disturbing effect. On the other hand the individual patient might find the reiterated testing increasingly annoying merely from repetition.

The study herein reported was made on 59 patients. All were males, the average age being 31 years and average period of hospitalization about 5 years. In a measure this represents special selection in that relatively recent cases predominated somewhat to the exclusion of those of long standing, the average period of hospitalization of schizophrenics in Massachusetts being about 11 years. They were further selected in that patients suffering from any organic disease recognizable by careful physical and laboratory

examinations were routinely excluded from the group, as were those over 50 years of age. None had received medication other than occasional cathartics or similar treatment for passing ailments within 3 months of the beginning of the study. A few patients were dismissed from the group after a preliminary period because of intractability. No data from this group are included in the present report. Special care was taken to make sure that we were dealing with cases of schizophrenia in contradistinction to other psychoses with schizoid coloring. The diagnosis in each case represented the unanimous judgment of three psychiatrists as well as two internists and two psychologists who were experienced in dealing with psychotic patients. The same diagnosticians divided the patients into subgroups, but in this latter procedure predominance rather than unanimity of opinion was held to be sufficient.

The composition of the group as to types was as follows: catatonics, 9; hebephrenics, 13; paranoids, 10; simples, 3; mixed, 14; and 10 unclassified.

For purposes of control we made determinations of the fasting sugar levels of 31 normal male subjects living in the hospital. As emphasized by Jenkins,²⁸ a first consideration of researches of this type is the possibility of systematic laboratory error.

Methods. The Folin-Wu (macro-alkalin-copper tartrate-colorimetric) method was used exclusively. All specimens of blood were obtained from a puncture of the median basilic vein in the cubital space of the forearm. Samples were taken only in the early forenoon after a 15-hour fast. The samples were collected in accordance with the following set schedule:

Collection.	Interval after the first collection.
1	...
2	15 days
3	2 months, 15 days
4	3 months
5	5 months, 15 days
6	6 months

A mixture of potassium oxalate and sodium fluorid was used as an anticoagulant. Sugar standards were accurately checked each time they were renewed and again titrated for deterioration at frequent intervals. All colorimetric readings and the calculations were made by Miss Ruggles under the supervision of Doctor Joseph M. Looney.

Results. The more salient findings of the study are set forth in Table 2. In the control subjects the average fasting blood-sugar level was 95.4 mg. per 100 cc. The lowest value was 80 mg. and the highest 109 mg. That is to say, all findings were within the conventional normal limits. The coefficient of variation was only 6.9 per cent, indicating a rather high degree of homogeneity of the raw data.

Each of the 59 patients was scheduled for 6 sugar determinations, *i. e.*, a total of 354 samples. Satisfactory samples, however, were obtained only in 347 instances. The 7 samples missed were so distributed as to make no significant difference in results. As shown by the table and as illustrated in Fig. 1, the average blood-sugar

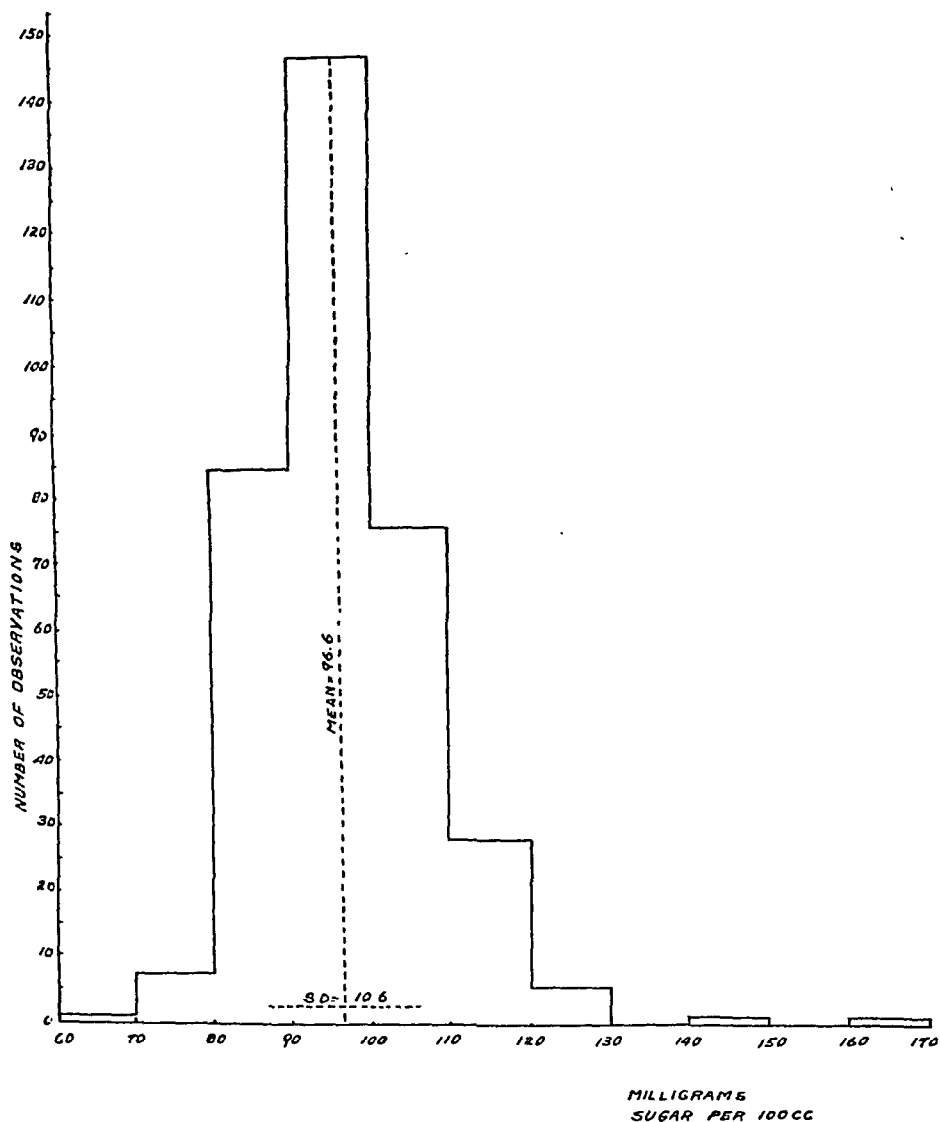


FIG. 1.—Distribution graph showing fasting blood-sugar levels in 347 tests on 59 patients.

level for all determinations was 96.6 mg. per 100 cc. as compared with 95.4 for our normal subjects. The lowest individual mean was 74 mg. and the highest 163 mg. Only 8 of the readings fell below 80 mg., *i. e.*, in the hypoglycemic range, and the same number above 120 mg., which conventionally marks the upper limit of normality. No individual patient was consistently hypoglycemic or hyper-

glycemic in all tests. Thus, 95 per cent of the total readings fell within the normal range. As shown by the coefficient of variation—11 per cent—the data were significantly less homogeneous than in the case of the normal subjects.

Subdividing the data in accordance with the schedule of collections they fall into three groups. In the first subperiod, the patients were relatively unaccustomed to being tested, whereas in the last

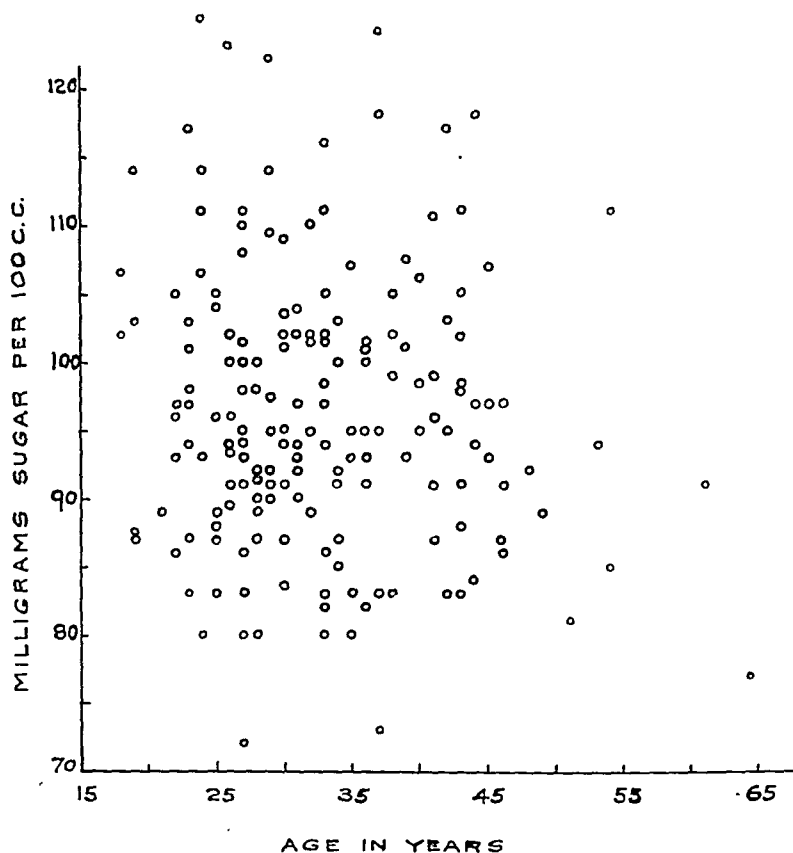


FIG. 2.—Scatter graph showing distribution of fasting blood sugar (mean values) in relation to age.

subperiod testing has become an old story. The suggestion was offered in an earlier paragraph that the average level of fasting blood sugar might be significantly affected by the factor of habituation. This suggestion is borne out by a comparison of results in the three periods. The average in the first instance was 99.3, in the second 96.5, and in the third 93.1 mg. per 100 cc., the individual tendencies falling in with the averages. It is probable, then, that this last value is the most characteristic for schizophrenia, as such.

TABLE 2.—CONSTANTS OF DISTRIBUTIONS PERTAINING TO FASTING BLOOD SUGARS.

	No. readings.	Min.	Max.	Range	Mean.	Standard deviation.	Coefficient of variation.
Normal controls (mg. sugar) . . .	31	80	109	29	95.40 \pm 1.20	6.60 \pm 0.85	Per cent. 6.9
Seven months' study							
Age (years)	59	19	45	26	30.98 \pm 0.94	10.73 \pm 0.67	34.6
Hospitalization (years)	59	0	21	21	5.18 \pm 0.47		
Observations on 59 patients (mg. sugar)	347	74	163	89	96.60 \pm 0.38	10.60 \pm 0.27	11.0
Range of fasting sugars (mg.) 1st period	56	0	38	38	10.57 \pm 0.77	8.58 \pm 0.55	81.17
Range of fasting sugars (mg.) 2d period	55	0	28	28	9.09 \pm 0.62	6.77 \pm 0.44	74.48
Range of fasting sugars (mg.) 3d period	59	0	36	36	8.02 \pm 0.53	5.99 \pm 0.37	44.7
Range of all values, 3 periods	56	10	78	68	25.39 \pm 0.96	10.64 \pm 0.68	41.9
All research patients							
Age (years)	193	14	61	47	32.47 \pm 0.40	8.18 \pm 0.28	25.2
Hospitalization (years)	193	0	25	25	4.80 \pm 0.22		
Initial fasting sugar values (mg.) . .	193	72	144	72	96.29 \pm 0.52	10.60 \pm 0.36	11.0

Inspection of Table 2 brings out another characteristic, the significance of which raises an interesting question. In each period 2 samples were taken at intervals of 15 days. The sugar values in some cases were identical in the 2 samples, but in others differed by as much as 38 mg. In the first period the range of variation was from 0 to 38 mg., with a mean difference of 10.6. In the second period the range was somewhat less and the average difference was 9 mg. In the third the range was about as in the first but the mean difference was further reduced to 8 mg. The most probable explanation of the decreasing variability from period to period, like that of the average sugar level, is habituation, *i. e.*, a lessening of the disturbing factor of emotional reactions to the test procedure.

If the time is extended to include all three periods, we have a maximal interval of 6½ months between individual tests and 6 tests included in each series. In this case, the dispersal becomes materially greater. The smallest difference between highest and lowest readings on the individual patient was 10 mg. and the largest 78 mg. The average difference between extreme values was 25.4 mg. That is to say, the difference was nearly 3 times as great with 6 readings as when 2 only were considered. This observation is presumably only a special case of the general law that when any function, subject to variation, is repeatedly studied, the range of the variation among findings increases to a maximum that mirrors the ultimate potentiality of the factors acting to produce changes.

Correlations. We have material available for a test of the influence of change of clinical state on the sugar level. The psychiatrists had rated all the patients studied into three categories: those whose clinical state improved, those in which it regressed, and those in which it remained essentially unchanged. Table 3 sets forth the data in a contingency table dealing with the blood sugar in these three categories. It is obvious that the changes in the sugar level in relation to changes in the clinical condition show a random dis-

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tribution. Hence, no relationship is evident between the depth of the psychosis and the sugar level.

TABLE 3.—RELATION OF CLINICAL CONDITION TO BLOOD SUGAR.

Fasting blood sugar.	Improved.	Regressed.	No change.	Totals.
Higher	1	1	8	10
Lower	4	3	25	32
No change	6	4	11	21
Totals	11	8	44	63

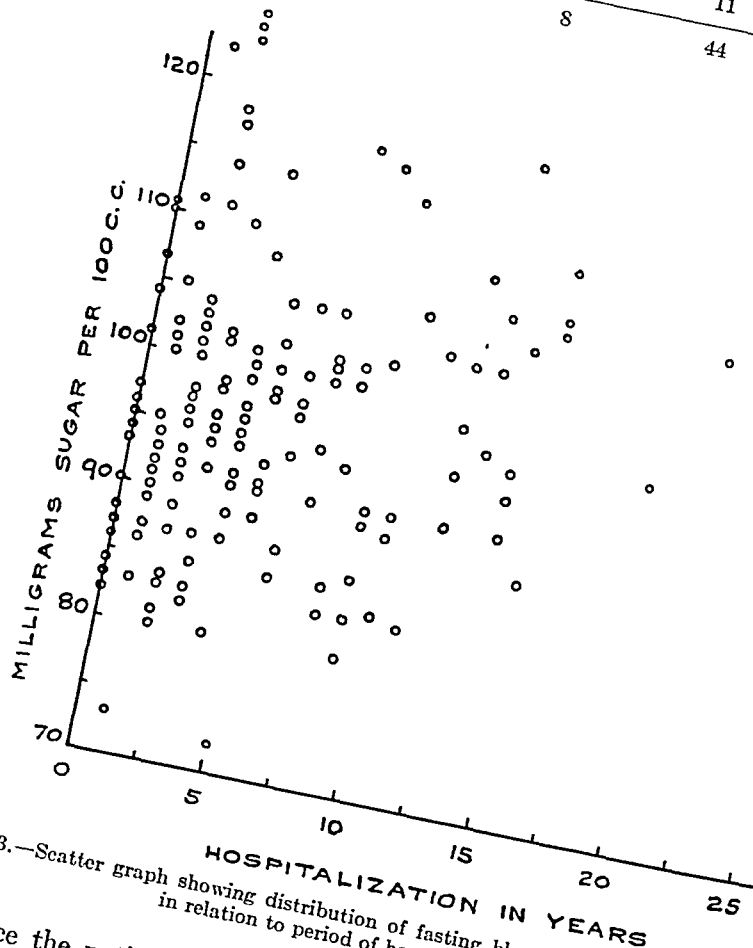


Fig. 3.—Scatter graph showing distribution of fasting blood sugar (mean values) in relation to period of hospitalization.

Since the patients studied by Sleeper and Hoskins²² were also male schizophrenics and since the methods used in their study were identical with those used in the present study, the two groups of data can be combined for purposes of statistical analysis. The first reading on each patient was utilized for this purpose. In the combined series we then had a total of 193 patients in whom the average age and average hospitalization period were not significantly

different from those making up our "Seven Months' Series." In the larger series, the average fasting blood-sugar level was 96.3 mg. and the standard deviation 10.6, values almost identical with those of the smaller group.

Effects of Age. Kooy⁹ as well as Raphael and Parsons²⁰ interpreted their data as indicating that the age of schizophrenic patients materially affects the blood-sugar level, the older showing a higher level than the younger. Despite the fact that the age range in our series was greater than in theirs, our results (Fig. 2) showed no correlation whatever.

Hospitalization Period. As Kooy⁹ has pointed out, it is reasonable to suppose that the longer a patient remains in an institution the more stabilized become his habits of exercise and diet. Hence, it might be expected that in time the sugar level would become stabilized at a minimal level. As shown in Fig. 3, our results in a larger group than Kooy's again failed to show any correlation between the period of hospitalization and sugar level.

Subtypes of Psychosis. Our "Seven Months'" patients, as previously noted, were divided into subgroups. Table 4 shows the average blood-sugar level for each group. The groups are too small to justify general conclusions but as far as they go they appear to indicate the highest level in the hebephrenics (99.5 mg. per 100 cc.) and the lowest in the catatonics (92.7 mg.), with the other groups falling in between.

TABLE 4.—RELATION OF TYPE OF PSYCHOSIS TO BLOOD SUGAR.

No. of patients.	Type.	Mean blood sugar.
9	Catatonic	92.7
13	Hebephrenic	99.5
10	Paranoid	96.3
3	Simple	95.8
14	Mixed	94.9
10	Unclassified	97.9

Summary. A study is presented of the fasting blood-sugar levels as disclosed by 6 samples taken at standard intervals from 59 male schizophrenic patients over a period of 6½ months.

In 95 per cent of 347 determinations the values lay between the conventional limits of normality, namely, 80 and 120 mg. per 100 cc. The average value was 96.6 as compared with an average of 95.4 mg. in 31 normal control subjects studied by the same technique. Eight readings were obtained in the hypoglycemic and 8 in the hyperglycemic ranges.

The variation among the schizophrenics was higher than that in the controls, as was shown by the coefficients of variation, 11 and 6.9 per cent, respectively.

The samples were collected in pairs at 15-day intervals with intervening periods of 2½ months. There was a consistent drop in

the average blood-sugar level from period to period, the first being 99.3 and the third 93.1 mg. per 100 cc. These findings suggest that habituation with a presumable lessening of emotional reaction to the test played a part in determining the sugar level.

The range of difference in consecutive tests also decreased consistently from one period to another; in the first the average difference was 10.6 and in the last 8 mg. per 100 cc.

No significant correlation could be recognized between the blood-sugar level and the age, period of hospitalization, or severity of the psychosis.

Of the subgroups, the hebephrenics showed the highest average level, namely, 99.7 mg., and the catatonics the lowest, namely, 92.7 mg.

Conclusion. Schizophrenia is characterized by normal fasting blood-sugar levels but the individual variability is somewhat greater than in normal subjects.

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STUDIES OF LIVER FUNCTION IN ADVANCED PULMONARY TUBERCULOSIS.*

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LESIONS of the liver are found almost constantly at autopsy in cases of advanced pulmonary tuberculosis.¹ Some of these consist of localized foci of tuberculosis; others show some degeneration, usually fatty or amyloid, but occasionally hyperplastic. Fatty degeneration particularly is considered a frequent and serious complication of tuberculosis.²

While these lesions have been widely recognized postmortem, it has not been easy to collect convincing evidence of hepatic insufficiency during life. The relative merits of the various laboratory tests of hepatic function are beyond the scope of this report, but it is well to bear in mind that no such test is widely recognized as detecting small lesions of the liver. The liver is a complicated organ. Its functions are numerous and relatively independent of one another, and the biliary functions may be seriously damaged without disturbing the metabolic functions; even the carbohydrate metabolism may be damaged without interference with the protein and fat metabolism. These considerations, and the large "factor of reserve" associated with the gland, explain to some extent why tests of hepatic function have not met with great clinical success.

Nevertheless the clinical detection of hepatic insufficiency in pulmonary tuberculosis has been attempted. Aubertin,¹ in a large series of cases studied with several liver function tests, found that in the progressively deteriorating cases the bad general condition and the hepatic insufficiency ran a remarkably parallel course.

Leuret and Aubertin³ studied 100 patients, basing their conclusions as to the presence or absence of hepatic insufficiency on clinical observation (symptoms) and on the laboratory tests of urobilinuria, the reaction of Hay, the elevation of the coefficient of Clogne-Derrien, or a slight glycuronic reaction of camphor. Many of the gastro-intestinal symptoms which were considered by these and other authors to be significant of hepatic insufficiency we now know from the work of Brown and Sampson might just as well have been due to intestinal tuberculosis. The presence of

* This study was aided by a grant from the Trudeau Foundation.

hepatic insufficiency was found to follow closely the course of the disease, and transient insufficiency was often accompanied by extensions of the disease.

The Present Study. Twenty-three patients with advanced tuberculosis (19 with far advanced and 4 with moderately advanced) were selected for studies of hepatic function. Five tests were used, the cinchophen oxidation test, the icterus index, the bromsulphalein test, the Congo red and the galactose test. Most patients received all of these tests; in fact some of them were repeated several times. Rarely were less than the five tests done on an individual patient; when hemolysis or a broken tube spoiled a test we did not urge patients unduly who feared venepuncture.

So that all tests might apply to the same clinical condition of the patient, they were completed on any given patient within a period of 2 weeks. It was only the coöperation of a large number of people which made this possible.*

Congo Red. The procedure used in this test was that described by Strasser⁴ and Wallace.⁵ A 1 per cent solution of the dye was injected in amounts of 0.25 cc. per kg. of body weight. Blood was withdrawn 4 minutes and 1 hour later. Using the first specimen as a standard, colorimetric comparison of the two samples gives the percentage decrease of dye in the plasma. The normal percentage decrease is 10 to 30 per cent. Many technical difficulties occurred in this work, such as hemolysis. In some cases we had to work with low colorimetric readings, which introduced a factor of error. Altogether we felt that the results were more interesting than satisfactory, and the work is reported only for the negative conclusion possible to draw from it. Seven of 19 patients showed readings above the normal of 30 per cent (from 33 to 51 per cent). Although all of these patients also had abnormal function, as evidenced by one or more other tests, these readings were obtained at a time when our calculated possible error could be as great as ± 15 per cent, and we are not inclined to attach much significance to them. In 7 patients in whom technical errors were rigidly excluded, the Congo red test showed no abnormality. We believe that this work shows that amyloidosis demonstrable by the Congo red test could not be proved in this series.

Cinchophen Oxidation Test. Lichtman⁶ described a test of hepatic function based on the oxidation of cinchophen. After ingestion of 0.45 gm. of cinchophen the excretion of oxycinchophen in the urine

* We are indebted to Dr. Robert Laidlaw for much of the work done with Congo red and to Mr. Carrol Stauff for the titrations in the galactose test. Dr. J. Woods Price, Medical Director of the Reception Hospital, Saranac Lake, kindly placed a number of patients at our disposal, and we are also grateful to Drs. Edgar Mayer and George Wilson for the use of 1 patient at the Northwoods Sanatorium, Saranac Lake. Mr. Donald Cummings, chemist of the Trudeau Foundation at the Saranac Laboratory, was extremely helpful in technical assistance. We are grateful to Miss Ophelia Sawtell for the coöperation of the nursing staff, and to Miss Virginia Reid for secretarial assistance.

TABLE OF COMPARATIVE LIVER FUNCTION TESTS.

Case No.	Ic-terus index.	Cincho-phen.	Brom-sulphalein.	Congo red, % decrease.	Galactose.		Ad-vance-ment of dis-ease.	De-gree of tox-emia.	Type of dis-ease.
					Concentration (parts per M.).	Out-put, gm.			
1	179 mg. 37.3%	5m—45% 30m—No trace	0	2h— 6.32 24h— 2.28	1.25 2.17	Far	0	P
2	13 mg. 2.8%	25	2h— 4.85 24h— 1.80	0.46 1.03	Mod.	0	P
3	133 mg. 27.7%	5m—25% 30m—No trace	4	2h— 5.58 24h— 1.87	0.76 1.33	Far	Mod.	E
4	3.0	205 mg. 42.6%	5m—30% 30m—Trace	..	2h— 1.13 24h— 0.88	0.64 1.06	Far	Mod.	P
5	3.2	259 mg. 54%	5m—35% 30m—No trace	22	2h— 3.37 24h— 1.18	0.54 1.36	Mod.	0	Pntx
6	3.6	277 mg. 57.8%	5m—30% 30m—No trace	26	2h— 7.42 24h— 3.43	0.24 0.64	Far	Sl.	Pntx
7	5.1	124 mg. 25.7%	5m—50% 30m—No trace	51	2h— 1.18 24h— 0.57	0.66 1.54	Far	Sl.	Thpl
8	6.6	203 mg. 42.3%	5m—40% 30m—Trace	38	2h— 2.08 24h— 1.02	0.29 0.48	Far	0	E
9	7.0	185 mg. 38%	5m—30% 30m—No trace	43	2h— 4.60 24h— 1.55	0.28 1.42	Far	Mod.	E
10	7.4	123 mg. 25.6%	5m—35% 30m—No trace	38	2h— 5.07 24h— 3.12	0.32 0.55	Far	0	E
11	7.4	128 mg. 26.7%	5m—35% 30m—No trace	39	2h— 4.00 24h— 1.18	1.48 2.32	Far	Sl.	E
12	7.5	128 mg. 26.7%	5m—50% 30m—Trace	23	2h— 5.28 24h— 1.66	0.82 1.58	Far	Sl.	E
13	7.7	126 mg. 26.6%	5m—45% 30m—Sl. trace	33	2h— 2.91 24h— 2.04	0.56 0.89	Mod.	0	Pntx
14	8.2	146 mg. 30.3%	5m—45% 30m—No trace	29	2h— 0.98 24h— 0.78	0.38 1.32	Mod.	0	P
15	8.5	151 mg. 31.5%	5m—30% 30m—No trace	20	2h— 2.56 24h— 1.66	0.26 1.46	Far	Extr.	E
16	10.0	56 mg. 11.6%	5m—40% 30m—No trace	..	2h—10.92 24h— 1.00	0.58 1.17	Far	Sl.	E
17	10.2	138 mg. 28.8%	34	2h— 2.40 24h— 1.02	0.68 1.75	Far	Mod.	E
18	11.1	5m—25% 30m—No trace	38	2h— 6.25 24h— 3.57	2.26 2.57	Far	Mkd.	E
19	12.4	92 mg. 19.4%	2h— 5.31 24h— 1.06	0.69 1.29	Far	Sl.	E
20	12.7	160 mg. 33.4%	5m—30% 30m—No trace	..	2h—17.50 24h— 2.34	1.78 2.52	Far	Sl.	Pntx
21	15	160 mg. 33.2%	5m—50% 30m—8%	11	2h—10.30 24h— 2.56	0.53 0.86	Far	Sl.	E
22	15.0	254 mg. 53%	5m—25% 30m—No trace	12	2h—10.29 24h— 1.39	1.09 1.68	Far	Sl.	P
23	16.0	47 mg. 9.8%	5m—20% 30m—No trace	20	2h— 1.87 24h— 0.53	0.40 0.93	Far	0	E
Upper normal limits . .	7.0	100	No definite amounts after 30 minutes	30	2h—10	2.00			

E = Exudative. P = Productive. Pntx = Pneumothorax. Thpl = Thoracoplasty.
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below 100 mg. has been found in normal subjects, while 100 to 150 mg. signify slight liver function disturbance. Results between 150 and 250 mg. signify moderate liver function disturbance, and results above 250 mg. indicate severe functional disturbance. Using the technique described by him we found that 18 of 22 patients excreted more than 100 mg. Eleven of these patients excreted more than 150 mg., and in 3 the excretion was above 200 mg. This test yielded more positive results than any other single test of hepatic function. It is hoped to examine this test as a possible indicator of the activity of a tuberculous process, comparing it with the criteria of activity now in use at the Trudeau Sanatorium.

Galactose Test. Induced galactosuria has recently been given much consideration as a test for hepatic function.

Olivier, Sliosberg and Desnos⁷ investigated liver function by the galactose test in 67 patients. Of 41 progressive patients, 32 (77 per cent) gave a pathologic reaction; of 25 patients that were in good general condition with a slight tendency toward progression, 12 (49 per cent) gave a pathologic reaction. Patients treated with gold salts did not give a pathologic reaction any more frequently than other patients. A point of particular interest was that all patients with gastro-intestinal symptoms gave a pathologic reaction.

In Thiébaud and Dieryck's² 11 patients the total elimination was often rather low; four times only did it surpass 3 gm., and in 3 patients it was below 1.5 gm. They believed, however, that such figures were not as important as the high level reached in the first fraction in betraying the inability of the liver to metabolize this amount of galactose. In 4 patients in which autopsy was obtained, histologic examination showed diffuse fatty degeneration, and in 3 of these patients, tuberculous foci. They found the test of prognostic value when repeated in the same patient. They agreed with Aubertin that dysfunction of the liver is frequent in tuberculosis and believe that the galactose test is the easiest and most valuable method of gaining this information.

Method Used. The technique used in our series was feeding 40 gm. of galactose in 200 cc. of water at 8 A.M., the patient having fasted since midnight and having voided at 7.45 A.M. The urine was then collected at 10 A.M., 12 NOON, 6 P.M., and the last specimen at 8 A.M. the following morning. During this time the fluid intake was restricted to 1500 cc. The various urine samples were examined for sugar, and the volume was determined. In accordance with the opinion that the concentration should be considered nearly as important as the total output, we have taken above 10 parts per 1000 for the first 2 hours, and a total output above 2 gm. as a pathologic reading. Among 23 patients, 7 gave pathologic readings.

Bromsulphalein Test. Two milligrams of bromsulphalein per kg. of body weight were injected intravenously. Blood was withdrawn from another vein after 5 minutes and after 30 minutes, and com-

pared with standards containing a known percentage of bromsulphalein. In the 20 patients submitted to the test no pathologic readings were obtained.

Icterus Index. The icterus index was satisfactorily determined in 20 patients after the exclusion of a few with whose sera we had some of the technical difficulties to which this test is subject. Readings of 7 or above were considered abnormal. Seven of these patients gave readings between 7 and 10; 8 gave readings between 10 and 16. One patient with an icterus index of 10 and a positive galactose test, who had far advanced exudative tuberculosis with bilateral cavitation, developed an acute appendicitis. Appendectomy had to be done and, while he stood the operation well, there was considerable postoperative bleeding, so much in fact that he had to be reopened. The surgeon failed to find any gross bleeding vessel and accepted latent jaundice as the probable explanation of the bleeding. There were no clinical signs of hepatic insufficiency.

Discussion. By the use of 5 different liver function tests, it is apparent that liver damage may be demonstrated according to the accepted interpretation of these tests in a high percentage of patients. Not every test was always positive in the same patient and it appears to be necessary to use several tests in order to demonstrate during life the liver damage which we know is so commonly found at autopsy. The bromsulphalein test gave us no assistance whatever. The icterus index was positive in 75 per cent of patients; the cinchophen oxidation test was positive in 81.8 per cent; the Congo red test did not give readings above normal in any of the group of patients in which the technique was most carefully controlled, and such readings as were above normal might possibly have been due to technical errors. The galactose test was positive in 30.4 per cent of patients. Two patients with moderately advanced tuberculosis and extreme prolonged digestive disturbances were included in this series because it has been said that the galactose test is always positive in patients having gastro-intestinal disturbances. These patients had had negative gastro-intestinal Roentgen ray films, also gall bladder studies, and had no intestinal tuberculosis as demonstrable by the technique of Brown and Sampson. Neither of them gave a positive galactose test, but both had a positive cinchophen test and one had an elevated icterus index. Though most of the patients in this series had an exudative type of lesion, we are unable to confirm the opinion that exudative lesions are likely to cause abnormal readings in the Congo red test. In fact we did not observe that exudative lesions even of the more intense type caused any particular test to give pathologic readings. The degree of toxicity of the disease as judged by clinical symptoms, for example, fever, tachycardia, night sweats, loss of weight, did not seem to have any relation to any particular test. It was interesting to observe that 3 patients with tuberculous empyema and

mixed infection of the pleural cavity gave pathologic readings only to the cinchophen test.

At the present time it would be more or less speculative to discuss a possible influence of hepatic insufficiency on such procedures as pneumothorax, gold therapy and thoracoplasty, but the fact that liver damage is demonstrable in such a high percentage of patients would seem to indicate that it should be given some consideration at least in the selection of patients for major operative procedures.

Case Abstracts. CASE 1.—A dentist, aged 46, began to cough and expectorate 8 years ago. He had an hemoptysis. He rested partially at home and returned to full time work in 6 months. Repeated Roentgen ray films showed no extension of the disease. He had a fistula in ano and an hemoptysis 2 years ago and stopped work. He had a moderate amount of dyspnea and gaseous indigestion. Two years ago a phrenectomy was done, about 6 months later he had another hemoptysis and pneumothorax was induced. The cavity was never completely collapsed. He had lost 20 pounds in weight and at the time of the tests was a bed patient, his temperature ranging from 96° to 99° F., his pulse from 56 to 88 and his sputum was Gaffky v.

CASE 2.—An Englishman, aged 54, had influenza in 1918 and a year later, *i. e.*, 13 years ago, a diagnosis of tuberculosis was made, based on positive sputum, cough, expectoration, night sweats, fever and hemoptysis, and he went to Albuquerque for a year. Eight years ago he had a serious relapse, including an attack of intestinal and laryngeal tuberculosis, and was treated at Mt. McGregor. His general condition improved so that his larynx is now healed. At the time of the tests his temperature ranged from 97° to 99° F., his pulse from 64 to 100 and his sputum was positive, Gaffky viii.

CASE 3.—A female, aged 32, developed laryngitis 9 years ago. Two years later this was diagnosed as tuberculous, and pulmonary tuberculosis was discovered. She was then at Trudeau Sanatorium for 3 years, during half of which time she worked. She made a good recovery and regained her voice. She then worked at home for 1½ years, but had a relapse of her pulmonary tuberculosis 2 years ago and rested at home. Six months ago her laryngitis recurred and there was a bilateral extension of the pulmonary tuberculosis. The tests were done just prior to the initiation of bilateral pneumothorax and her temperature ranged from 96.2° to 101.4° F., her pulse ranged from 80 to 108 and her sputum was negative.

CASE 4.—A male, aged 25, developed catarrhal symptoms 22 months ago. He was admitted to Trudeau with involvement of both lungs to the 3d rib and bilateral cavitation. Because of massive hemoptyses pneumothorax was begun on the right to control the bleeding 18 months ago. His temperature then was 103.6° F., and pulse 140, but subsided within 3 weeks. Pneumolysis was done 16 months ago. Following an attack of persistent vomiting during the course of positive pressures, he developed a spontaneous pneumothorax a year ago. Hemopneumothorax followed and the patient was desperately ill and tuberculous empyema followed. Because of extremely toxic symptoms which gomenol failed to control, open drainage was instituted 6 months ago and mixed infection, of course, followed. At the time of the liver function tests the daily maximum temperature was 100° F., and pulse 108.

CASE 5.—A male, aged 23, consulted a doctor 1 year ago because of rattling in the left chest. Diagnosis was established at that time. He never had any toxic symptoms at any time. On admission 11 months ago

his Roentgen rays showed a slight lesion of the right apex, and on the left side infiltration to the 3d rib with cavity 2 cm. in diameter in the apex. Seven months ago he was given pneumothorax treatment because of an increase in the size of his cavity. Although only moderately advanced he was included in this series because of long-standing persistent nausea, anorexia and loss of weight for which no adequate cause could be found. Gastro-intestinal series and gall bladder films were negative. He had no toxic symptoms at the time of the liver function tests.

CASE 6.—A male aged 30, had a hemoptoic onset of his disease $2\frac{1}{2}$ years ago. He was a bed patient until his admission to Trudeau, having had two relapses before admission, the latter of which proved to be spontaneous pneumothorax. The disease was of very light intensity in the right lung, radiating from the root into the deeper portions of the lung. The left side showed cavity formation in addition to the spontaneous pneumothorax. The patient never made any marked improvement but continued greatly underweight with occasional elevations of temperature and pulse. There was tuberculous empyema with mixed infection. At the time of the liver function tests his temperature ranged to 101.3° F. and pulse to 100. He was also having hematuria and acid-fast bacilli were present in the urine.

CASE 7.—A male, aged 25, had a hemoptoic onset of his disease 21 months ago. On his first admission to Trudeau 20 months ago he had elevation of temperature and pulse, and several hemoptyses totaling 38 ounces. His Roentgen ray films showed, on the right, infiltration radiating from the root into the deeper portions of the lung; left, infiltration to the 3d rib. Because of massive hemorrhages he was given pneumothorax on the left almost at once. A rectal abscess developed and healed. Tuberculous empyema developed with temperature to 104° F. and pulse to 140. Seven months ago he had recovered sufficiently to permit of a thoracoplasty and, in spite of postoperative infection, his clinical condition at the time of the liver function tests was fairly good. His temperature reached 99° F. daily, and his pulse 90.

CASE 8.—A female, aged 25, developed pleuritic symptoms 6 years ago. A diagnosis of lobar pneumonia was made. It soon became evident, however, that the disease was tuberculosis and she rested for $1\frac{1}{2}$ years. She returned to work, but 6 months later relapsed. On admission to Trudeau 15 months ago she had fever to 100° F., pulse to 116 and Roentgen ray films showed a small amount of infiltration in the middle third on the right and, on the left, infiltration throughout with cavity formation 5 cm. in diameter in the upper third. She was given pneumothorax at once on the left, but developed a serious extension of the disease in the right base with marked symptoms of toxemia. By means of pneumolysis, the cavity on the left closed and the disease on the right showed progressive healing, so that at the time of the liver function tests the patient was in fair clinical condition, although still confined to bed. Her temperature was frequently elevated to 99.4 and 99.6° F. and her pulse still frequently reached 96.

CASE 9.—A male, aged 44, had been ill for the past 6 years, part of which time he was able to work. His toxic symptoms included intermittent night sweats and loss of weight. During these 6 years his disease showed a progressive increase in both lungs, so that when admitted 2 months ago there was infiltration on the right side with cavity 3 by 3 cm., and infiltration on the left side to the 5th rib with cavity formation in the upper third of various sizes. There was also laryngeal tuberculosis. His maximum temperature was persistently 99.6° F. Pneumothorax was begun on the left 6 weeks ago, with a fairly satisfactory collapse and an improvement on the opposite side, including reduction in the size of the cavity. Slight elevation of temperature to 99.2° F. persisted, however, at the time of the liver function tests.

CASE 10.—A female, aged 21, developed acute symptoms resembling pulmonary abscess $4\frac{1}{2}$ years ago. Diagnosis of tuberculosis established by sputum examination at that time. She was in bed for 7 months and in the following 2 years had two relapses. Pneumothorax treatment was started on the left 22 months ago; 20 months ago she had pneumonia on the right, and 19 months ago developed a pleural effusion on the left. She improved symptomatically following this and was practically without symptoms on admission a month ago, at which time it was decided to do a thoracoplasty on the left because of failure of the pneumothorax to collapse large cavities in the upper lung. She had no toxic symptoms at the time of the liver function tests, which were done just prior to thoracoplasty.

CASE 11.—A female, aged 25, developed dry pleurisy 3 years ago, but made a complete recovery. She developed marked fatigue 18 months ago, followed by hoarseness and, for a period of 2 weeks, complete aphonia. She had chills and fever to 104.6° F., at which time tuberculosis was diagnosed. Pneumothorax was begun on the right before her admission to Trudeau 11 months ago. The left lung at the time of her admission showed infiltration of an exudative character in the lower three-fourths. In spite of this very extensive disease her progress in the sanatorium has been fairly satisfactory as a bed patient. At the time of the liver function tests, her fever rose occasionally to 100° F. but for the most part ranged around 99.2° F., and her pulse rate reached a maximum daily average of 100.

CASE 12.—A male Italian, aged 18, noticed a year ago that he had unusual dyspnea while swimming. A month later he began to cough and expectorate, and tubercle bacilli were found in his sputum. He came to Saranac Lake at that time and pneumothorax was induced soon afterward because of the extent and character of the disease and the presence of active symptoms (night sweats, cough, expectoration, hoarseness and fever). Pneumolysis was necessary to secure an effective collapse and after 5 months his symptoms subsided. At the time of the tests his general condition was good. His sputum was positive, Gaffky vi.

CASE 13.—An American housewife, aged 27, had a pleuritic onset 7 years ago which recurred every winter since then, and was accompanied by cough, fatigue and indigestion. She was never very ill, however, and a diagnosis of tuberculosis was not made until 3 years ago, when a Roentgen ray was taken. She was kept in bed 5 months and then given pneumothorax treatment on the right. A complete collapse was obtained, and 11 months later the patient came to Trudeau without symptoms except for severe chronic indigestion which was of 5 years' duration. The course of her disease in the sanatorium was uneventful except for the persistence of severe indigestion. Gastro-intestinal films were negative. Gall bladder films were negative and intestinal tuberculosis could not be demonstrated according to the technique of Brown and Sampson. She was included in these studies because of the impression that such cases of unexplained, persistent, severe indigestion always give a pathologic result to the galactose test. Her temperature and pulse were normal; she was 12 pounds underweight and her sputum was Gaffky i at the time of the tests.

CASE 14.—An American, aged 20, had bronchopneumonia with pleural effusion 17 months ago. He had fever for 3 weeks with night sweats, cough and expectoration. A diagnosis of tuberculosis was made and he came to Saranac Lake a year ago, and was kept in bed. He improved constantly, gaining 75 pounds, partly with the aid of insulin. Six months ago he was allowed up, but 2 months later he had an influenza-like attack and a Roentgen ray showed that a cavity had reopened. Since that time he has been in bed and improving. His temperature at the time of the tests ranged from 96.6° to 98.8° F., pulse from 60 to 100.

CASE 15.—A male, aged 50, past history includes lues and amputation of a finger for destructive osteomyelitis. His tuberculosis began 2 years

ago with a loss of 32 pounds of weight and occasional night sweats. At that time he had bilateral involvement and ran a high fever for a long time. He came to Saranac Lake 6½ months ago and since that time has had marked gastro-intestinal symptoms and fever to 103° F., night sweats and hemoptyses, which symptoms persisted at the time of the liver function tests. He also had mild tuberculous laryngitis. The liver edge was palpable 2 cm. below the costal margin.

CASE 16.—A male, aged 24, had an insidious onset of his disease 2 years ago. Three months ago he had a cold and pleurisy with fever to 101° F. This was followed by an hemoptysis and fever to 104° F. On admission to Trudeau 6 weeks ago he had fever to 99.4° F., pulse to 120, and had a far advanced lesion on the right side to the 5th rib, with a cavity 2 cm. in diameter, and on the left side a lesion to the 7th rib with a cavity 4 cm. in diameter in the middle third. Comparison with films taken 7 weeks previously showed an extension of the disease in both lungs. Films taken 1 month after admission showed extension of the disease in the right lung. At the time the liver function tests were done he had mild symptoms of toxemia and just after the completion of the test bilateral pneumothorax was instituted.

CASE 17.—A female, aged 23, developed catarrhal symptoms 5 years ago and came to Saranac Lake 4 years ago, at which time she had fever, night sweats, loss of strength and weight and hoarseness. She had been constantly a bed patient, her disease intermittently improving and progressing. She was found to have a hypothyroidism with a basal metabolic rate of -30. At the time the liver function tests were done she was about to undergo oleothorax treatment. She was still a strict bed patient. Her daily maximum temperature was 100° F., her pulse 110 and marked fatigue was present.

CASE 18.—A male, aged 26, was perfectly well until 8 months ago. He then developed catarrhal symptoms and loss of weight. He had fever to 99.4° F. He came to Trudeau 3 months ago with fever at that time to 100.2° F.; white blood cells, 11,300; sedimentation rate, 14. Roentgen rays showed infiltration radiating from the root into the middle third on the right, and on the left infiltration to the 5th rib with a cavity 3 by 4 cm. The lesion was exudative. Pneumothorax was begun at once. Two months ago pneumothorax was begun on the right due to an increase of infiltration with development of cavity. At the time of the liver function tests the patient was quite toxic, his maximum temperature ranging from 99.4° to 103.1° F.

CASE 19.—A female American, aged 31, began to cough and expectorate, and grew hoarse 16 months ago. Tubercle bacilli were found in the sputum 13 months ago; 9 months ago she began to experience fatigue, and for 2 months prior to the tests she had a few night sweats. At the time of the tests her temperature ranged from 97° to 99.2° F., her pulse from 72 to 108. She had laryngeal tuberculosis and her sputum was positive, Gaffky viii.

CASE 20.—A male, aged 23, developed catarrhal symptoms 17 months ago, with some hoarseness, loss of strength and temperature to 102° F. for several days. His Roentgen rays showed a lesion of slight intensity on the right side to the 2d rib and on the left side an exudative lesion throughout the lung. Pneumothorax was begun on the left 7 months ago. Since that time his progress has been slow, but showed consistent improvement. He remained in bed during this time, and at the time when the liver function tests were done his daily maximum temperature averaged 99.2° F., and pulse 110.

CASE 21.—A male, aged 29, had rectal abscess 2½ years ago, and catarrhal symptoms 2 years ago followed by hemoptysis. Roentgen rays showed involvement of both lungs, and he spent 10 weeks in the Catskill Mountains. Five months ago he had another hemoptysis, since which time he has been

in bed. Pneumothorax was started $3\frac{1}{2}$ months ago for control of persistent bleeding. During this time the temperature ranged from 100° to 103° F. He lost 10 pounds in weight and had night sweats. His disease at this time spread to the right lung, so that when admitted to Trudeau $2\frac{1}{2}$ months ago he had far advanced tuberculosis with practically no symptoms. At the time of the liver function tests the patient had lost his toxic symptoms but was still confined to bed.

CASE 22.—An American, aged 34, had an acute pneumonic onset $4\frac{1}{2}$ years ago, at which time he had pleural effusion. He has coughed and expectorated since that time and his fever did not completely subside for 6 months. His sputum was found positive 6 months after the onset. He had one hemoptysis and came to Saranac Lake $3\frac{1}{2}$ years ago. Five months after arrival pneumothorax was begun and continued 21 months. A 75 per cent collapse was obtained which did not, however, close the cavity; fluid developed, and the air pocket was lost. His general condition was unfavorable at the time the tests were done. His temperature ranged from 97° to 99.4° F., his pulse from 68 to 108 and his sputum was positive, Gaffsky vii.

CASE 23.—An Englishman, aged 34, was well until he had an influenza-like attack 6 months ago. He returned to work but never regained his strength, and a morning cough and expectoration persisted. Three months ago he felt feverish and had some night sweats, and consulted his doctor. The diagnosis of tuberculosis was made and the patient was sent to Saranac Lake, where pneumothorax was begun 2 months ago. His condition was good at the time of the tests, temperature ranging from 97° to 99° F., pulse from 68 to 88 and sputum was positive, Gaffsky vii.

Conclusions. In a series of 23 patients having advanced pulmonary tuberculosis all but one gave pathologic readings in one or more of a group of 5 tests of hepatic function. Of the tests used, the cinchophen test, the icterus index and the galactose test were the most sensitive in the order named.

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LIVER FUNCTION IN CATARRHAL JAUNDICE.

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THERE are admitted to the medical service of every hospital a number of subjects having a painless type of regurgitational jaundice. This group includes several clinical entities, such as carcinoma of the head of the pancreas, salvorsan hepatitis, and

acute yellow atrophy. There remain a number of subjects having an acute jaundice in whom no etiologic agent can be found, and in whom the jaundice spontaneously subsides. To such cases the term catarrhal jaundice is applied. Eppinger² says that "every case of jaundice with a sudden onset lasting 1 to several weeks, giving a favorable prognosis, should be included in the group of 'icterus catarrhalis' providing the diagnosis cholelithiasis can be ruled out." Klemperer, Killian and Heyd³ followed Eppinger by including in the term "icterus catarrhalis" such diverse conditions as: Icterus due to obstruction of the common bile duct following gastro-intestinal catarrh; icterus due to degeneration and multiple areas of necrosis of the liver, and icterus due to cholangitis. Blumer⁴ believes catarrhal jaundice to be the sporadic form of epidemic infectious jaundice, the pathology of which was described by Symmers⁵ as consisting of acute necrotic changes of the polygonal liver cells without evidence of cholangitis or biliary obstruction. Symmers noted the similarity of this disease and acute yellow atrophy. It is not surprising, since the clinical term "catarrhal jaundice" is represented at necropsy by diverse pathologic findings, that some investigators, including Eppinger,² Blumer,⁴ Baehr and Klemperer,⁶ Jones and Minot,⁷ and Moschcowitz,⁸ should consider some cases of catarrhal jaundice as examples of acute yellow atrophy that spontaneously recover.

On reviewing the published results of liver-function tests in cases of catarrhal jaundice, it is obvious that the conditions would vary from catarrhal swelling at the duodenal papillæ to an acute necrosis of the liver cells. The functional conditions vary from a retentional to a regurgitational jaundice; from absent bile in the intestines to an increased amount throughout the disease; from no alteration in liver function, except icterus, to a profound disturbance comparable to that found in acute yellow atrophy. Jones and Minot⁷ showed by means of duodenal washings that there was marked diminution of the bile entering the intestinal tract during the first or obstructive phase of the disease. Wallace and Diamond⁹ by means of the urobilinogen test demonstrated a phase of the disease that was characterized by little or no bile entering the intestinal tract. Mjassnikôw and Tschilipenko,¹⁰ however, consider catarrhal jaundice to be characterized from the very beginning by a high urobilinuria. It is evident that the clinical label of "catarrhal jaundice" is applied to dissimilar pathologic or physiologic disturbances. Its evaluation has been rendered more difficult by the great rarity of opportunities for anatomical study of the tissues involved. This study was made to define the pathologic and physiologic features more accurately and to establish criteria for diagnosis in this group of subjects.

Selection of Cases. The subjects of this investigation were patients on the wards of the Third (New York University) Medical and Psychiatric Divisions of Bellevue Hospital. During the period of this study 81 sub-

jects were discharged with the diagnosis of catarrhal jaundice. Of this group 30 individuals were subjected to an intensive liver-function study. The subjects selected were adults below 40 years of age with no history, clinical signs or serologic evidence of syphilis, no history of alcoholism, or taking of drugs for the relief of arthritic or neurotic pains (due to possibility of cinchophen or similar poisoning). The jaundice had been acute in onset, painless in character and of short duration. Complete physical, Roentgen ray, serologic and laboratory studies were made. Subjects who were found, after the completion of our investigations, to have another somatic disease, even if it was thought to be unrelated to jaundice, were excluded from this report as were also all subjects who left the hospital before they were sufficiently recovered to confirm the diagnosis.

As a result of this selection of cases only 19 of the 30 subjects studied form the basis of this paper.

The Liver-function Tests Used. 1. Serum bilirubin was determined qualitatively and quantitatively, using Hall's¹¹ modification of the van den Bergh technique. The serum bilirubin was judged by the following criteria: 0.5 mg. per cent or less, normal; 0.51 to 2 mg. per cent, latent jaundice; 2.1 mg. per cent or over, clinical jaundice.

2. Daily urobilin determinations were made by the method of Wallace and Diamond⁹ on a freshly voided specimen of urine collected at approximately the same time each morning. Recognition of urobilin in dilutions greater than 1 to 20, or its complete absence from the urine, was considered abnormal.

3. A qualitative bilirubin determination was performed using Ehrlich's diazo reaction on the same specimen of urine.

4. The original bromsulphalein method of Rosenthal and White¹² was followed for the dye test. The percentage of dye remaining in the blood stream 30 minutes after intravenous injection of 2 mg. per kilogram body weight was determined. The presence of a measurable amount of the dye (5 per cent) at this time was considered abnormal.

5. The levulose tolerance test was performed as soon as practical after the patient was admitted to the hospital, and repeated again before discharge. Occasionally, intermediate tests were performed, but an interval of 7 days or more was allowed between tests. This period was found by Jolliffe¹³ to be of sufficient duration to obviate the first or prior test influencing the succeeding tests, as found by Lennox and Bellinger,¹⁴ if the tests followed each other at short intervals. Prior to the test the patients were fasted for 14 hours and the test carried out as in a previous study.¹⁵ The criterion established by Jolliffe,¹³ namely, a rise in blood sugar to or over 125 mg. per cent, following the administration of a weighed amount of levulose by mouth, was considered abnormal.

Results. It was concluded early in this investigation that in a majority of subjects we were studying the same entity through several stages. A uniform pathologic and physiologic picture was presented by 16 of the 19 subjects (Cases 1 to 16), which we will designate the "typical group," while the remaining 3 gave findings at variance with those in this group. It was found convenient at the completion of the study on each subject to designate the day on which the maximum concentration of serum bilirubin was found as the "0" day; prior days were labeled as "-5, -4, -3," etc., and days following 0 day were designated as "+1, +2, +3," etc. A very different pathologic and physiologic picture was observed to precede the 0 day, as compared with the subsequent picture.

TABLE 1.—CONDENSED DATA OF 2 TYPICAL AND 3 ATYPICAL CASES.*

Case No.	Days of jaundice before start of study.	Day.†	Uro-bilinogen.	Bile in urine.	Qualitative van den Bergh.	Serum bilirubin, mg. per cent.	Brom-sulphalein, per cent retention.	Levulose tolerance. Blood sugar, mg. per cent.			
								Fast-ing.	30 min-utes.	60 min-utes.	120 min-utes.
1	4	-4	0	+	Imm.	8.2	35	98	120	142	190
		-2	0	+	Imm.	9.1	40				
		0	0	+	Imm.	10.1	50				
		+1	1:4	+	Imm.	8.1	30				
		+2	1:160	+	Imm.	5.0	25	100	113	130	175
		+3	1:32	+	Imm.	2.6					
		+4	1:16	+	Imm.	2.1					
		+5	1:4	0	Del.	1.8	10				
2	15	+7	1:2	0	Del.	1.6	0	100	116	110	98
		+8	1:4	0				
		-7	0	+	Imm.	11.1	100				
		-3	1:2	+	Imm.	12.7	100				
		-2	0	+	Imm.	13.0		83	100	98	83
		-1	0	+	Imm.	13.8					
		0	1:30	+	Imm.	14.5	100				
		+1	1:90	+	Imm.	10.0					
17	1	+2	1:60	+	Imm.	8.1	90	86	100	72	68
		+4	1:10	+	Imm.	4.1	35				
		+7	1:5	0	Imm.	2.2	10				
		+11	1:8	0	Imm.	1.8	F. T.				
		-2	1:16	0	Del.	5.6	15	105	236	151	153
		-1	1:16	0	Del.	5.8	15				
		0	1:20	0	Del.	6.0					
		+1	1:50	0							
18	2	+2	1:16	0	Del.	4.0	5	83	97	105	90
		+3	1:16	0	Del.	3.0					
		+4	1:10	0	Del.	1.2	0				
		+5	1:8	0				
		-11	1:4	+	Imm.	3.0	0	83	80	117	80
		-9	1:60	+							
		-8	1:2	+	Imm.	3.3	0				
		-6	1:8	+							
19	0	-2	1:30	+	Imm.	3.2	0	62	66	80	92
		-1	1:4	+							
		0	1:2	+	Imm.	3.8	0				
		+1	1:2	+							
		+2	1:10	+	Imm.	3.0	0				
		+3	1:1	+	Imm.	2.6					
		+4	1:1	+	Imm.	2.2					
		+6	1:4	0	Del.	1.8					
		-10	1:8	+	Imm.	2.2		67	77	68	65
		-7	1:30	+	Imm.	2.4	0				
		-3	1:16	+							
		-2	1:16	+	Imm.	3.5	0				
		-1	1:20	+	Imm.	3.6	0				
		0	1:8	+	Imm.	3.7	0				
		+1	1:32	+	Imm.	3.0	0				
		+3	1:40	+	Imm.	2.7					
		+5	1:75	+	Imm.	2.5					
		+7	1:16	+	Imm.	2.3					
		+9	1:25	+							
		+11	1:75	0	Imm.	2.0					
		+12	1:25	0							
		+14	1:2	0	Del.	1.1	0				
		+16	1:4	0				

* To conserve space only Cases 1 and 2 of the 16 cases in the typical group are tabulated. Only a sufficient number of the daily observations are tabulated to illustrate the trend of the tests.

† The day on which the maximum concentration of serum bilirubin occurred was designated as the 0 day; prior days were labeled as -5, -4, -3, etc., and days following the 0 day were labeled as +1, +2, +3, etc.

Serum Bilirubin. The serum bilirubin, as measured by the quantitative van den Bergh reaction, is tabulated for each individual in the accompanying table. The composite bilirubin curve of the typical group is presented in Fig. 1a. In each subject there occurred a progressive rise in serum bilirubin until the maximum, which we have designated as the 0 day, was reached. The duration of the jaundice from time icterus was noted by the patient to the height of the jaundice averaged 11 days and varied from 3 to 24 days. In each subject in the typical group following the 0 day there occurred a precipitous fall in the serum bilirubin for 3 to 5 days. In the composite curve (Fig. 1a) the bilirubin fell during a 4-day period from 11.1 to 5.2 mg. per cent, almost a 50 per cent fall. During this period observers, not cognizant of the degree of icterus as measured in the laboratory, at times remarked that the jaundice was increasing and only very occasionally noted a decrease, indicating that marked quantitative changes can occur in the serum bilirubin, particularly toward improvement, before this fact can be noted with any degree of accuracy by the observer at the bedside.

Although the serum bilirubin falls rapidly at first, it is not until the +13 day that the composite curve comes within the range of latent jaundice. In every instance the level of latent jaundice was reached by the +24 day, and in one instance by the +2 day. The average duration of jaundice from onset to latent jaundice was 24 days, varying from 8 days (Case 17) to 49 days (Case 4). In the typical group Case 3 was of the shortest duration, 11 days from onset to latent jaundice. The icterus of the skin does not completely disappear by the time latent jaundice is reached, due possibly to the fact that the skin is so stained by the bile pigment, that days or weeks may be required for the pigment to be carried away by the blood or by the desquamation of the epidermis.

The qualitative van den Bergh reaction in the typical group was always of the immediate direct variety during the height of the disease, and, as a rule, when the serum bilirubin was above 2 mg. per cent. In one exception (Case 11) the reaction became delayed at a level of 2.5 mg. per cent. In Subject 17, one of the atypical group, there was a delayed direct reaction even when the serum bilirubin was 5.6 mg. per cent. This subject had, at no time, an increased fragility of the red blood corpuscles to hypotonic saline, abnormal bleeding or coagulation time, or an increase in reticulated red blood cells. Bile was always absent from the urine. In this connection, when bile was present in the urine, the van den Bergh reaction was always of the immediate direct variety. On the other hand, bile may be absent from the urine and the van den Bergh may be of the immediate direct variety. A possible explanation is that the "renal threshold" for immediate direct reacting bilirubin becomes elevated above the conventional 2 mg. per cent level, if the subjects have a jaundice of longer than average duration.

Bile disappeared in the urine while the serum bilirubin level was between 2.1 and 3 mg. per cent in 4 subjects; between 3.1 and 4 mg. per cent in 4 subjects; and at 5.1 mg. per cent in 1 subject. The duration of the jaundice in this group of 9 subjects was 30 days, while in the remaining subjects of the typical group the average duration was 15 days and the average height of the icterus was

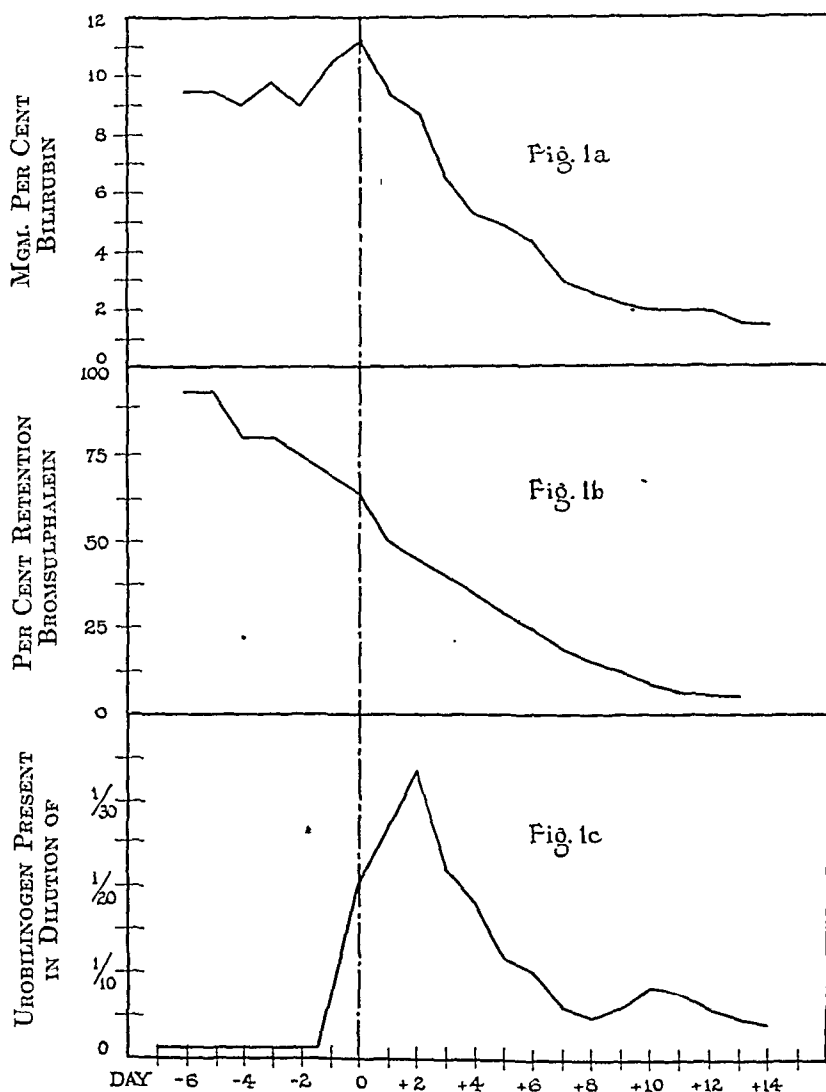


FIG. 1.—The composite serum bilirubin, bromsulphalein, and urobilinogen curves in the typical group.

12.8 mg. per cent on the 0 day as compared to 8.3 mg. per cent in the remaining cases. These facts suggest that a severe icterus, if continued for some time, may cause renal damage.

We have observed that the output of phenolsulphonaphthalein in cases suffering from jaundice may be markedly impaired. Bartlett¹⁶ has recently described certain patients who are jaundiced or have

recently been jaundiced and who show a constant inability to excrete phenolsulphonephthalein and to concentrate the urine. He also notes the development of anuria in 2 subjects during jaundice, in whom, 2 weeks prior to onset of the anuria, "the urine was microscopically and chemically normal and the excretion of phenolsulphonephthalein was above 75 per cent."

Urobilin. In the typical group the amount of urobilin in the urine varied with the stage of the disease (Fig. 1c). Prior to the 0 day urobilin was absent or present only in traces. The complete absence of urobilin for 10 consecutive days never occurred. Two subjects showed complete absence for 8 consecutive days, otherwise complete absence never occurred longer than 7 consecutive days. On the 0 day or +1 day urobilin suddenly appeared in the urine in increased amounts. The average critical dilution (Fig. 1c) rose to 1 to 35 on the +2 day and fell to 1 to 20 on the +4 day. This sudden increase in urobilin in catarrhal jaundice heralds the rapid recovery of the patient. Following the +4 day the urobilin as a rule is present in normal amounts and in no subject was it increased after the +6 day. In the atypical group (Cases 17 to 19) a period of absent urobilin was never noted.

Bromsulphalein. Dye retention paralleled the serum bilirubin in the individual subject. The maximum retention of bromsulphalein occurred on or prior to the 0 day. In the composite curve (Fig. 1b), dye retention fell from 90 per cent on the -6 day to 65 per cent on the 0 day, due to the addition of a greater number of subjects as the 0 day was approached. Following the 0 day the fall in dye retention roughly paralleled the fall in serum bilirubin and fell below the 5 per cent level on the +13 day, at the same time as the serum bilirubin well within the range of latent jaundice. On the +14 day dye retention was *nil* in all except one subject, in whom there was a 40 per cent retention. Ten days later the retention of dye in this subject had fallen to 5 per cent. In the atypical group, 2 cases (18 and 19) had no retention of the dye, and in the third (Case 17) there was only a very slight retention.

Levulose Tolerance Test. The levulose tolerance test was performed 40 times on the 19 subjects. The test was performed on or prior to the 0 day on each subject. In the typical group, 14 of the 16 subjects (87.5 per cent) showed a positive tolerance test during this stage of the disease. Subjects 2 and 16 had normal curves. If the severity of the disease can be judged by the intensity of the jaundice, Subject 2 had a severe and Subject 16 a mild attack of catarrhal jaundice. The composite curve of the typical group (Fig. 2a) during this stage had a fasting level of 97.8 mg. per cent blood sugar. This compares with a fasting level of 88.7 obtained in this laboratory in 81 tests on 49 normal subjects (Fig. 2c).¹³ The composite curve rose to 120.8 at the 30-minute period and 132.3 at the 60-minute period, compared to 98.8 and 97.2 at the same

periods in normal subjects. At the 120-minute period the composite blood sugar was 122.4 mg. per cent as compared to 87.6 in normal subjects. The tolerance to levulose was, therefore, in the composite, and in 14 of the 16 individual subjects distinctly abnormal by exceeding the upper limits of a normal response, namely, 125 mg. per cent of blood sugar. In the atypical group, Subject 17 showed an abnormal response, while Subjects 18 and 19 showed normal curves.

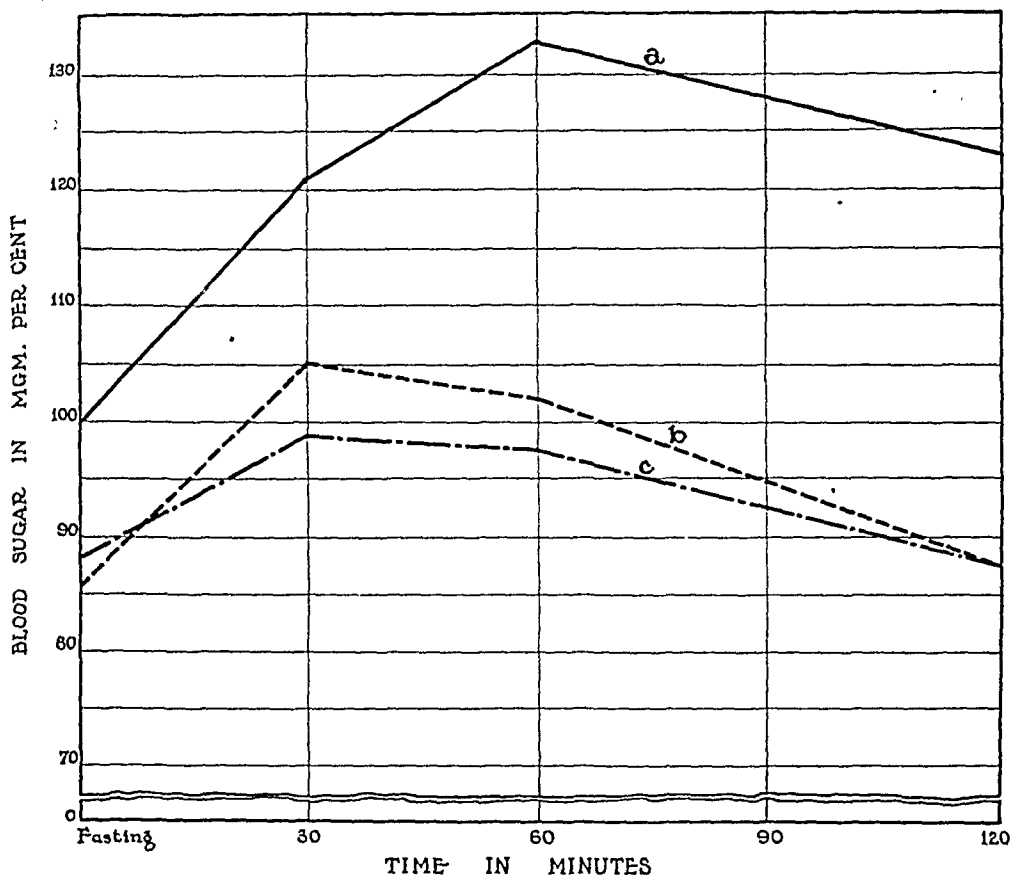


FIG. 2.—Composite levulose tolerance curves. *a*, Typical group prior to the 0 day; *b*, typical group following the 0 day; *c*, average of 81 tests on 49 normal subjects.

Following the 0 day 24 tests were performed on the 19 subjects. Of these tests 3 were positive. Subject 1 on the +1 day showed a positive curve, the blood sugar reaching 175 mg. per cent at the 120-minute period, but on the +8 day the test was normal. Subject 10 on the +3 day had a positive levulose tolerance test in that the blood sugar rose to 135 mg. per cent at the 120-minute interval, but by the +11 day the test was normal. Subject 4 on the +13 day had a slightly abnormal tolerance in that the blood sugar rose to 129 mg. per cent at the 60-minute period. However, on the +24 day the curve was normal. Every subject, therefore, except Case 4, showed a normal levulose tolerance test after the +4 day. The

exception had an unusually severe and prolonged attack of catarrhal jaundice. Every subject eventually showed a normal response to levulose, which fact serves as a control to the tests performed prior to the 0 day. These observations (Fig. 2) indicate that prior to the 0 day subjects of catarrhal jaundice usually, though not invariably, have a diminished tolerance to levulose. This impaired tolerance returns to normal on recovery of the patient. An insufficient number of tests were performed during the first 4 days following the 0 day to draw conclusions on the levulose tolerance during this stage of the disease. The two subjects tested during this period had abnormal curves, which may or may not be the typical finding during this period.

Discussion. Our results indicate that there are at least 3 pathologic groups included under the clinical term of "catarrhal jaundice." The typical group, represented by 16 of 19 of our cases, has a form of regurgitational jaundice¹ which runs through 3 phases. The first phase is characterized by a rapidly increasing icterus, absent or diminished urobilin in the urine, a high retention of bromsulphalein, and usually, though not invariably, a positive levulose tolerance test. This period can be called the "obstructive phase." The second phase lasts for about 4 days, and is characterized by the sudden appearance of urobilin in the urine in normal or excessive amounts, a rapid fall in serum bilirubin, and in bromsulphalein retention. This stage can be called the "critical phase." The third phase begins when the urobilin returns to normal and lasts on an average for 9 days; it is characterized by the gradual return of all functions toward normal and the rapid improvement of the patient. This stage can be called the "recovery phase."

The total duration of the jaundice in the typical group varied from 11 to 49 days, averaging 24 days. In Jones and Minot's⁷ series of 23 cases, the jaundice lasted for 14 days or less in 12 subjects and for more than 2 months in 4 subjects. In the typical group the jaundice lasted for 14 days or less in only 3 subjects, and no subject had jaundice for over 2 months. The short duration of the jaundice in this series of cases should be noted in view of the fact that no treatment was directed toward its relief.

Our subjects 18 and 19 were totally dissimilar from the typical group; they have only a mild degree of icterus, a normal levulose tolerance test and an unimpaired ability to excrete bromsulphalein. In no part of their course was there an "obstructive" or "critical phase." This type of jaundice is frequently seen in the Out-Patient Department and is of such a mild character that the patient seldom enters the hospital. One could advance the argument that they are mild cases of the type of jaundice found in the typical group, but the total dissimilarity, especially the absence of an obstructive phase, makes it likely that these 2 cases represent a different entity.

The type of case represented by Subject 17 probably represents a third entity. The jaundice was of the retentional type¹ as evidenced by the absence of bile in the urine and the delayed direct van den Bergh reaction. The levulose tolerance was positive and a slight retention of bromsulphalein was present. The urobilin was normal throughout, except on 1 day. The clinical picture presented by this subject was not unlike that presented by the typical group.

The total dissimilarity of functional tests in the conditions reported in the literature as catarrhal jaundice shows the need for establishing criteria for this diagnosis. Many varieties of acute hepatitis of unknown etiology are clinically similar but unrelated in terms of alteration in function. An acute retentional jaundice with absent bile in the urine and a delayed direct van den Bergh reaction, a regurgitational jaundice characterized by a hyperurobilinuria throughout its course, and a regurgitational jaundice characterized by an obstructive, critical and recovery phase must be dissimilar entities, no matter how similar they may be to the bedside observer. We believe that the entity represented by our typical group, namely, a regurgitational jaundice of acute onset running through three fairly distinctive phases of: (1) obstruction; (2) crisis, and (3) recovery with characteristic laboratory findings in each, deserves the distinction, at present, of a definite label, and that it is to this group alone that the term "catarrhal jaundice" should be applied. It is suggested that the remaining cases be designated as an acute hepatitis of unknown etiology with regurgitational or retentional jaundice, as the case may be, until a larger group has been studied and a better description of them has been made.

Summary. 1. In 19 cases of the type customarily regarded as catarrhal jaundice it has been found that a definite pathologic and physiologic syndrome was present in 16 of the 19. This consists of a regurgitational jaundice which runs through three distinct stages:

(a) An "obstructive phase" with an average duration of 11 days in which there is a progressive deepening of the icterus, absent or mere traces of urobilin in the urine, a retention of bromsulphalein paralleling the degree of jaundice and, usually (87.5 per cent), a positive levulose tolerance test.

(b) A "critical phase" with an average duration of 4 days in which urobilin suddenly appears in the urine in high normal or definitely elevated amounts, a coincident abrupt fall in serum bilirubin and bromsulphalein retention.

(c) A "recovery phase" with an average duration of 9 days during which time the serum bilirubin falls within the level of latent icterus, urobilin is present in the urine in normal amounts and the tolerance to levulose and the retention of bromsulphalein return to normal.

The term "catarrhal jaundice" should be limited to subjects showing this pathologic and physiologic syndrome.

2. The 3 remaining cases were of distinctly different pathologic and physiologic types. It is suggested that these types may be appropriately designated as acute hepatitis of unknown etiology with, as the case may be, retentional or regurgitational jaundice.

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UPPER LOBE BRONCHIECTASIS.*

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IN the differential diagnosis of pulmonary tuberculosis considerable significance is ascribed to the site of the lesion. Upper lobe lesions are considered tuberculous unless proven otherwise; lower lobe lesions are considered non-tuberculous unless tubercle bacilli are present in the sputum. Although this generalization holds in the majority of instances in which the diagnosis is open to question, a greater degree of accuracy could be attained if more emphasis were placed on the possible non-tuberculous character of upper lobe disease in which tubercle bacilli are persistently absent from the sputum. Individuals who give a history of cough and expectoration for a number of years without symptoms or signs suggestive of pulmonary neoplasm and who, on physical and Roentgen examination reveal upper lobe involvement, should be suspected of having

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a bronchiectatic condition, provided of course that the sputum does not contain tubercle bacilli.

Bronchiectasis limited dominantly, or entirely, to one or both upper lobes of the lungs is not so rare a condition as might be thought considering the scant mention it receives in the literature. At necropsy on opening the chest, the pleura, over the upper lobes that are the seat of bronchiectatic changes, is almost invariably adherent to the chest wall. The lungs, on cut surface, reveal dilatation of the bronchi leading to one or both upper lobes and, at the periphery of the lung, emphysematous blebs of varying size may be discerned. The former, on superficial examination, may be mistaken for tuberculous cavities; the latter, for spontaneous pneumothoraces. The very large dilatations frequently involve the terminal ramifications of the bronchi near the periphery of the lung. When the walls are unusually thinned out, they themselves may be confused with emphysematous blebs. Macroscopic and microscopic study usually differentiates these conditions. The parenchyma of the affected part of the lung is fibrotic and atelectatic while other parts are distinctly emphysematous.

It must be stated at the outset that bronchiectasis of the upper lobes is, in the majority of instances, the result of a healed tuberculosis although specific elements may be lacking even on microscopic examination of the tissues: a fact true of nearly all long standing tuberculous fibrosis of the lung. To be sure fibrosis, *per se*, even that found in an upper lobe, is not invariably an indication of a pre-existing tuberculosis. In some patients, as will be shown later on, the clinical course of the disease, and the presence of fibrocalcific or fibrocaseous nodules in other parts of the lung, suggest that tuberculosis existed previously. In other patients, particularly young persons in whom a history of respiratory infections in childhood is elicited, there is an equal likelihood that the bronchiectatic condition is the result of a non-specific pneumonitis, as is often true in basilar forms of bronchiectasis. In either event, apparently, the process of pulmonary fibrosis and shrinkage produces traction dilatation of the bronchi, the condition being aided by the fixation of the lung to the chest wall. In some lungs, however, the degree of bronchial dilatation is out of proportion to the extent of the peribronchial fibrosis. It is possible that secondary infection of the deeper layers of the bronchial wall may be a factor in the causation of the ectasia. In addition, the constant cough with its attendant rise in intrabronchial pressure very likely plays a significant rôle. Although each of these factors has been considered at one time or another the chief causative agent in the production of bronchiectasis, it is the prevailing authoritative opinion that no single factor explains the condition entirely.

Report of Cases. CASE 1.—J. S., a man, aged 69, gave a history of "pneumonia" 25 years prior to admission. Since then he coughed and

expectorated sputum which was occasionally bloody. He worked all this time. About a year prior to admission he became increasingly more dyspneic, lost weight and his expectoration became more profuse especially in the recumbent position. Physical and Roentgen examinations were characteristic of advanced pulmonary tuberculosis with cavity formation in both upper lobes and emphysema of the lower lobes. There was an associated pulmonary osteoarthropathy of the phalanges of both hands. The sputum was negative for tubercle bacilli on 18 examinations. During his hospital stay of about 2 years his temperature ranged from 97° to 99.5° F. and his chief symptoms were cough, expectoration, increasing dyspnea and cyanosis. He died suddenly October 4, 1930. The lungs, at autopsy, revealed bilateral saccular bronchiectasis in both upper lobes and extensive bronchitis. The right lung, in addition, revealed several large emphysematous blebs on the pleural surface. There was no evidence macroscopically or microscopically of tuberculosis in the lungs or in the other visceral organs. The right auricle and ventricle were hypertrophied and dilated and the coronary arteries sclerotic (Fig. 1).

CASE 2.—Y. R., a woman, aged 49, was always in good health until about a year before admission. She complained of asthmatic seizures occurring chiefly at night and characterized by dyspnea and orthopnea lasting several hours. Physical and Roentgen examinations revealed changes that were interpreted as characteristic of fibrotic pulmonary tuberculosis with a cavity in the apex of the right lung. At the hospital, she continued to have paroxysms of dyspnea at irregular intervals which were not relieved by adrenalin. Intramuscular injection of sterile milk as well as injections of parathyroid hormone were of no avail. Examination of the sputum on 6 occasions, including 1 with antiformin, failed to reveal tubercle bacilli. The patient died of right heart failure 5 years after admission. Necropsy revealed bronchiectasis in both upper lobes. Numerous emphysematous blebs were prominent over the upper portions of the lungs, the remainder of the lungs revealing marked emphysema. The heart was hypertrophied and dilated while the visceral organs showed evidences of chronic passive congestion. There was no evidence of pulmonary tuberculosis on gross or microscopic examination of the lungs and other viscera. Microscopic examination revealed marked dilatation of the bronchi with secondary infection, but no tuberculous granulation tissue was found in the sections.

CASE 3.—B. O., a woman, aged 72, when admitted gave a history of cough and expectoration of about 20 years' duration, more severe in the preceding 5 years. On many occasions the sputum was streaked with blood. Physical examination revealed changes not unlike those of chronic fibrotic pulmonary tuberculosis of the right upper lobe with cavity formation. The sputum was negative for tubercle bacilli on 4 examinations. The patient remained in the hospital about 14 months when she developed an infection of the lower lip. This was soon complicated by general sepsis which terminated fatally within a few days. Section of the lungs revealed two of the bronchi leading to the right upper lobe to be markedly dilated at the terminal ends. None of the bronchi of the lower lobes or of the left lung was affected. Both lungs, in addition, were the seat of an embolic pneumonia with abscess formation. No tuberculous changes were found in the lungs or in any other organs of the body.

CASE 4.—B. R., a man, aged 66, gave a history of cough and expectoration for about 12 years prior to his admission. He was told he had pulmonary tuberculosis 4 years after the onset of his symptoms and he spent some time in health resorts. The physical and Roentgen findings were attributed to chronic fibrocaceous pulmonary tuberculosis with cavity formation involving both lungs. There was evidence of considerable fibrosis and pleuritis. The sputum was negative for tubercle bacilli on 12

occasions, including antiformin examination. He died suddenly 17 months after admission to the hospital. Postmortem examination revealed dense fibrosis and anthracosis in both upper lobes with many bronchiectatic dilatations. In the lower lobes, there were a few small fibrocaseous nodules. Aside from generalized arteriosclerosis which also involved the coronary arteries, there were no striking abnormalities found in the other organs excepting the brain. This organ revealed petechial subarachnoid hemorrhages. Microscopic examination of the lung revealed areas of fibrosis and round-cell infiltrations with several encapsulated foci.

CASE 5.—D. B., a man, aged 55, was admitted to Montefiore Hospital with a history of cough, dating 10 years, productive of thick mucoid expectoration. Lately, the cough had increased in severity and the patient had been growing weaker and had lost weight. Three years prior to his admission to the Tuberculosis Division, he developed cervical lymphadenopathy and splenomegaly. This was diagnosed as chronic lymphatic leukemia and he was treated with radiotherapy. Six months before his admission he had several copious pulmonary hemorrhages. Physical and Roentgen examinations of the chest revealed findings that were interpreted as due to moderately advanced pulmonary tuberculosis involving both upper lobes. The sputum was negative for tubercle bacilli on 4 examinations. He died about a month after admission to the hospital. Necropsy revealed dilatation of the bronchi of both upper lobes and bronchiectatic cavities. Emphysematous blebs were present over both apices. There were several scarred areas but no evidence of active pulmonary tuberculosis was discernible on gross or microscopic examination of any of the viscera. The lower lobes of both lungs were the seat of a terminal coalescing bronchopneumonia. The lymph nodes showed evidences of leukemic changes.

CASE 6.—C. T., a man, aged 51, had had a non-productive cough about 12 years prior to his admission. Later, there was an increase in the expectoration and at one time he spat blood. He also stated that 20 years previously he had "stomach trouble." During his stay at the hospital he had, on occasions, pain in the abdomen that was not related to the intake of food. His pulmonary condition was attributed to chronic pulmonary tuberculosis. The sputum was negative for tubercle bacilli on 4 examinations. He died 2 months after admission. At necropsy, the upper lobes of both lungs were the seat of anthracotic and atelectatic changes, the scarred areas containing numerous small bronchiectatic cavities all lined with thin, smooth, glistening membrane. The bronchi of the other lobes were moderately dilated. No active tuberculous caseation was noted. The stomach contained a carcinoma which had metastasized to the peritoneum and at one point had eroded the wall of the stomach causing a generalized peritonitis. The neoplastic condition was not suspected during life and was accidentally discovered at the autopsy.

CASE 7.—A. C., a woman, aged 52, had "pneumonia with pleurisy" at the age of 34. She dated her present illness, characterized by cough and expectoration, for a period of about 10 years. In the preceding 2 years she had a few copious hemorrhages. She was in several tuberculosis institutions before her admission to the Tuberculosis Division of Montefiore Hospital. Here the physical and Roentgen findings were considered typical of inactive fibrotic pulmonary tuberculosis with cavity formation. A particularly careful study was made of the sputum. On 10 occasions, including several antiformin tests and inoculation of the sputum into 2 guinea pigs, tubercle bacilli could not be demonstrated. In view of our recent experiences, the patient was presented by one of the authors to the staff conference as a case of upper lobe bronchiectasis possibly associated with emphysematous blebs. This diagnosis was confirmed a year later at the necropsy, the patient having died with signs of right heart failure. Over both upper lobes, particularly

the right, there were several large emphysematous blebs. The pulmonary tissue was fibrotic and the seat of many dilated bronchi in both upper lobes. The right ventricle of the heart was hypertrophied and there was congestion of the abdominal viscera. No changes characteristic of tuberculosis were found anywhere in the body, either on gross or microscopic examination of the tissues (Fig. 2).

CASE 8.—W. G., a man, aged 67, was admitted first to the Cancer Division of Montefiore Hospital with a history that about 9 years previously he began to have abdominal colic and vomiting. He was treated in several hospitals, improved and remained well for the following 6 years. Later, these symptoms recurred. The impression of the staff physicians was that the patient had a penetrating gastric ulcer rather than a cancer, although the latter was not wholly excluded. At this time, also, physical and Roentgen examinations revealed a condition that appeared quite characteristic of bilateral pulmonary tuberculosis with cavity formation. The sputum, however, was negative on 2 examinations. The patient improved and was discharged after a stay of 2 months.

Four years later, the patient applied for readmission, this time to the Tuberculosis Division. His history revealed that since discharge he had increasing dyspnea, chest pains, cough, expectoration and weakness. He had few complaints referable to the abdomen. He was examined by both authors in the Tuberculosis Clinic of the hospital and the impression was that the patient was not suffering from active pulmonary tuberculosis but of a fibrotic condition of both upper lobes and bronchiectasis. He was readmitted with the view of having lipiodol studies of the upper lobe bronchi but this was found impracticable. At the hospital, physical and Roentgen examinations, although quite consistent with a diagnosis of advanced pulmonary tuberculosis, were interpreted as due to upper lobe bronchiectasis that was probably associated with emphysematous blebs. The sputum was negative for tubercle bacilli on 6 examinations. Guinea pig inoculations of the sputum gave also negative results. The patient died rather suddenly about 3 weeks after his readmission.

The postmortem examination of the lungs revealed, in brief, the following: The parietal pleura over both upper halves of the lungs was adherent. Section of the right and left lungs revealed essentially a similar picture. The parenchyma in both upper lobes was considerably shrunken and fibrotic and contained numerous bronchiectatic cavities. Aside from some bronchial dilatation in fibrotic upper portions of both lower lobes, the remainder of the lungs did not show bronchiectatic changes. There were no areas of caseation or tubercle formation in the upper lobes but in the lower lobes there were present small caseous nodules, each surrounded by a fibrous capsule. Emphysematous blebs of varying sizes were distributed along the free borders of both lungs. Over the right upper and left lower lobes these blebs were considerably larger, measuring from 2.5 to 3 cm. in diameter. Ten sections of the lung studied by Dr. C. Spark revealed microscopically marked dilatation of the bronchi, pulmonary emphysema with bleb formation and fibrotic tubercles in the lower lobes. A healed ulcer was found in the stomach with resulting hour-glass contraction of the viscus. The other organs showed no significant changes (Figs. 3 and 4).

Synopses of Cases Reported in the Literature. The literature on upper lobe bronchiectasis is rather meager but the few descriptions that are on record make up in interest what they lack in numbers. The following résumé is appended as a source of reference rather than as a complete review of the literature. Although we have been able to find only 16 instances of upper lobe bronchiectasis, there is



FIG. 1.—Case 1, J. S. Numerous, smooth-walled cavities, continuous with bronchi in the upper lobe.



FIG. 2.—Case 7, A. C. Numerous thin-walled rarefactions are visible in the right upper lobe (bronchiectatic cavities and emphysematous blebs). Moderate fibrosis in the remainder of the lung. No pulmonary tuberculosis.



FIG. 3.—Case 8, W. G. Extensive pulmonary fibrosis with areas of rarefaction in both upper lobes (bronchiectasis and emphysematous blebs).

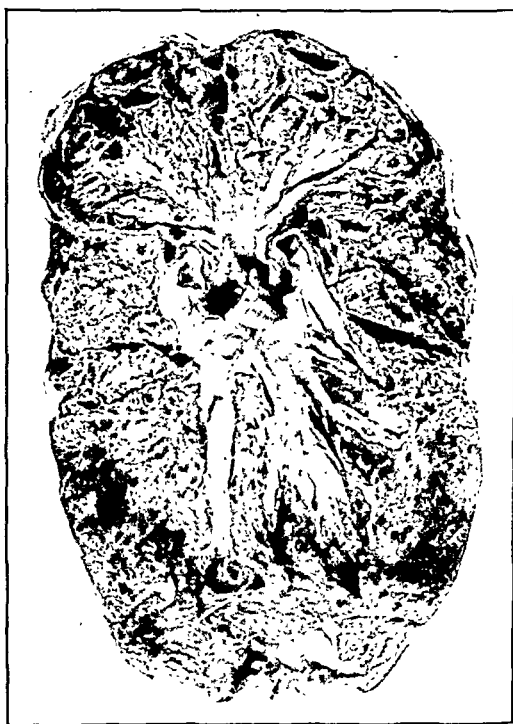


FIG. 4.—Case 8, W. G. Extensive fibrosis and bronchiectatic cavities in the upper lobe. Some bronchial dilatation in fibrotic areas in the upper portion of the lower lobe. Emphysematous blebs (not clearly seen in the photograph) on the pleural surface. Occasional encapsulated tubercle in the lower lobe.



FIG. 5.—Moderate dilatation of the bronchi leading to the right upper lobe (lipiodol injection).

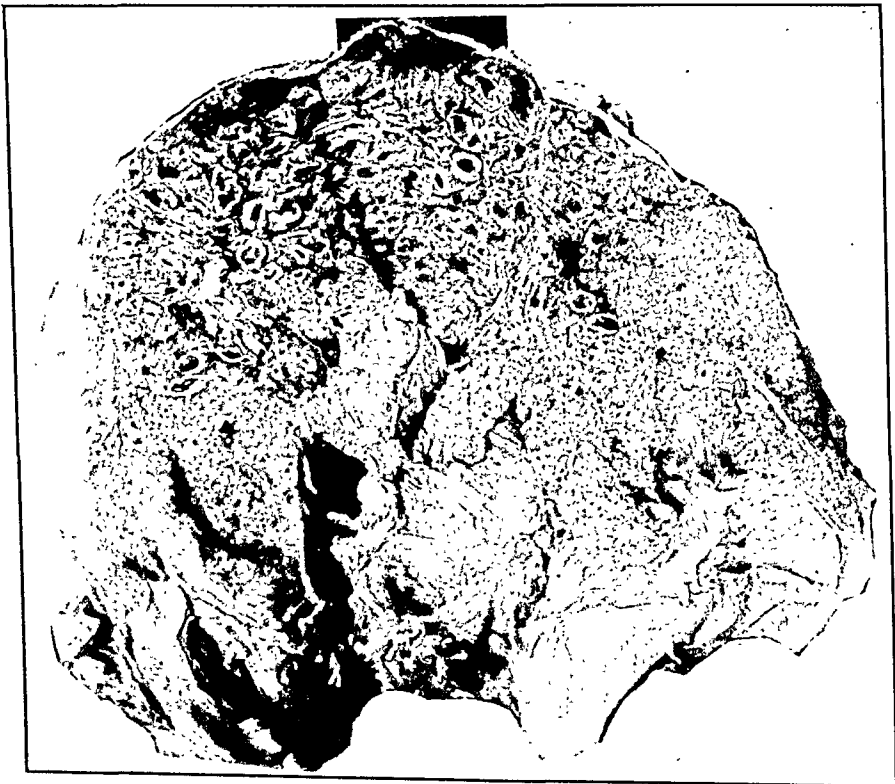


FIG. 6.—J. L. Extensive fibrosis and bronchiectatic cavities in the upper half of the lung and miliary tuberculosis in the lower half.

no doubt that many more have been described which we have overlooked. Studies on the lobar distribution of bronchiectasis, as observed at autopsy, occasionally include instances in which one or both upper lobes are the only ones involved. But apparently such instances are accidental discoveries, unaccompanied by clinical symptoms of any significance.

CASE 1.—A laborer, aged 59, complained of pulmonary catarrh since infancy, with cough, expectoration but no hemorrhage. Clinically, he was considered tuberculous. Autopsy revealed extensive bronchiectasis of both upper lobes, chiefly the right, with no evidences of tuberculosis (Louis¹).

CASE 2.—A man, aged 29, was admitted with a history of bronchitis of 2 years' duration. He had seromucous expectoration that was fetid. Examination revealed signs of cavitation in both upper lobes. The condition was diagnosed as upper lobe bronchiectasis. The patient died suddenly and autopsy confirmed the diagnosis (de Cérenville²).

CASE 3.—A well nourished woman, aged 25, had a left-sided pneumonia at 11. She had cough, bloody expectoration of nauseous taste and profuse sweating. It was suspected she had dilated bronchi rather than tuberculosis. Autopsy revealed extensive bronchiectasis of both upper lobes, chiefly of the right, with no evidences of tuberculosis (Greenhow³).

CASE 4.—A girl, aged 22, gave a history of illness of 3 years' duration following an attack of bronchitis. Because of the convulsive, pertussis-like cough and absence of tubercle bacilli in the sputum, the diagnosis of upper lobe bronchiectasis of the right lung was made. The patient improved with medication (Bruce⁴).

CASE 5.—A man, aged 53, presented symptoms and signs suggestive of pulmonary tuberculosis. From the character of the cough and expectoration and particularly the absence of tubercle bacilli in the sputum, a diagnosis of right upper lobe bronchiectasis was made. Autopsy confirmed the diagnosis (Sottas⁵).

CASE 6.—A woman, aged 58, always in good health, was admitted with a history of illness dating 5 months. She had cough, expectoration and repeated hemorrhages. Tuberculosis was suspected clinically. Autopsy revealed extensive bronchiectasis limited to the right upper lobe. No tuberculosis was seen (Bensaude⁶).

CASE 7.—A man, aged 62, was treated first in the clinic for bronchitis. Later, he developed pulmonary tuberculosis in the left upper lobe and, still later, in the right upper lobe. At this time, tubercle bacilli were found in the sputum. Two years before death he developed tuberculosis of the larynx. Autopsy revealed bilateral upper lobe bronchiectasis in association with healed pulmonary tuberculosis and infiltrative tuberculous laryngitis. No tubercle bacilli were found in the tissues on microscopic examination of the lung (Hauser⁷).

CASE 8.—A cachectic, anemic woman, aged 56, had copious, fetid expectoration that did not contain tubercle bacilli. A clinical diagnosis of unresolved influenzal bronchopneumonia and gangrenous cavity was made. At autopsy there was found bronchiectasis of the left upper lobe which was probably on the basis of a healed pulmonary tuberculosis (Bramwell⁸).

CASE 9.—A 33-year-old epileptic became ill with cough, fever, slight expectoration, dyspnea and loss of weight. No tubercle bacilli were found in the sputum. The patient died of a profuse pulmonary hemorrhage. Autopsy revealed bronchiectasis of the right upper lobe with an aneurysmal dilatation of one of the vessels, the source of the hemorrhage. The diagnosis was not made during life (Bauer⁹).

CASE 10.—A girl, aged 16, suddenly became ill with fever. On the basis of his previous experience, Bauer diagnosed the pathologic changes in the left upper lobe as caused by bronchiectasis. The sputum was negative for tubercle bacilli. The tuberculin test was negative. The patient was treated for a time with pneumothorax and did well (Bauer¹⁰).

CASE 11.—A girl, aged 13, had been ill several years previously with acute lobar pneumonia of the right upper and left lower lobes, which condition resolved by crisis. The sputum contained pneumococci but no tubercle bacilli. Three years later, she was in good health but examination revealed pathologic changes in the right upper lobe. The sputum was negative. The condition was considered tuberculous. The patient died of an accident. Autopsy revealed bronchiectasis of the right upper lobe with no evidence of tuberculosis (Wingfield¹¹).

CASE 12.—A man, aged 62, gave a history of chronic cough for many years. On admission he had cough, expectoration, hemorrhage, dyspnea and loss of weight from 220 to 175 pounds. He was sent to a sanatorium. On his return the impression was that he had a localized non-tuberculous fibrosis of the right upper lobe with some bronchial dilatation. This condition was verified at autopsy. There were no evidences of pulmonary tuberculosis. McCrae and Funk describe 4 other instances of upper lobe bronchiectasis in association with ulcerative pulmonary tuberculosis with cavity formation (McCrae and Funk¹²).

CASES 13 to 15.—Three patients are reported, ranging in age from 22 to 38 years, who had histories of preceding non-specific pneumonitides and whose sputum did not contain tubercle bacilli. Bronchographic examination with lipiodol revealed upper lobe rarefactions which the author ascribed to bronchial dilatations (Knüppel¹³).

CASE 16.—A woman, aged 28, had pneumonia in childhood. She had cough and bloody expectoration. The sputum was negative for tubercle bacilli. Bronchographic examination with lipiodol revealed some 50 cavities with fluid levels in the bronchi of the right upper lobe (Wood¹⁴).

Diagnosis of Upper Lobe Bronchiectasis. Bronchiectasis should be suspected whenever a patient with a long standing history of cough and expectoration reveals upper lobe lesions in the absence of tubercle bacilli in the sputum on repeated examination. Profuse expectoration, fetid breath, clubbing of the fingers and bouts of fever, classical symptoms in patients with suppurative lower lobe bronchiectasis, are unusual when the upper lobes alone are involved. This is probably due to the better drainage from the latter. Symptomatically, patients with upper lobe bronchiectasis present a picture of chronic fibroid tuberculosis. Increasing dyspnea and weakness, subnormal temperature, blood spitting or frank hemorrhage are characteristic. Tuberculosis of the larynx and intestines occasionally occur in patients with chronic fibroid tuberculosis.¹⁵ They are not present in the bronchiectatic stage of the disease. Right heart failure, coronary occlusion or non-tuberculous bronchopneumonia terminate the disease in the majority of instances.

The physical examination of patients with upper lobe bronchiectasis is of some help in differential diagnosis and probably more so than is the Roentgen film. The reverse is more often the case in active pulmonary tuberculosis. Fishberg¹⁶ has emphasized that in upper lobe bronchiectasis there is occasionally elicited resonance

above the clavicles; a rare occurrence in intensely chronic and long standing pulmonary tuberculosis. Likewise, in upper lobe bronchiectasis signs of apical shrinkage are often lacking; an unusual occurrence in tuberculosis. This may possibly be due to the fact that the largest dilatations of the bronchi are frequently situated subpleurally and the coëxistence of large air-containing emphysematous blebs give a resonant, at times, a tympanitic note on percussion. In some patients, rather than retraction, there is distinct cushion-like bulging of the supraclavicular fossæ. If the pleura is not particularly opaque to the Roentgen ray, one can sometimes discern small circular areas of rarefaction underneath. In this respect a Bucky film is helpful. Occasionally, too, thin-walled emphysematous blebs of varying size can be visualized on a well taken film, but, unless one thinks of upper lobe bronchiectasis the Roentgen configuration can be easily mistaken for tuberculous changes. An important point in differential diagnosis is that in spite of increasing symptoms which the patient may present, comparative films even after a lapse of several years may show surprisingly little change.

Next to the absence of signs of shrinkage of the apex, an important feature of the condition is the absence of tubercle bacilli in the sputum. The presence of active pulmonary tuberculosis makes, of course, any bronchiectatic changes of secondary clinical importance, regardless of the extent of the latter. Although physicians are fully aware of the diagnostic importance of the presence of tubercle bacilli in the sputum, they do not appreciate fully the significance of the absence of tubercle bacilli in the sputum. Persistently "negative" sputum is of greater value in differential diagnosis than is generally appreciated. In a recent study,¹⁷ one of us found that in 99 per cent of patients with advanced pulmonary tuberculosis, tubercle bacilli could be demonstrated in the sputum if at least 3 consecutive examinations were made. In the remaining 1 per cent the patients had chronic or acute miliary tuberculosis, fibrotic acinar nodular tuberculosis, therapeutic or tuberculous pneumothorax or massive pleural effusions. Pinner and Werner,¹⁸ in a study of more than 500 adult patients with active pulmonary tuberculosis, including a considerable number with minimal disease, found tubercle bacilli in over 99 per cent. The diagnostic significance of "negative" sputum cannot be over-emphasized. With the few exceptions noted, the persistent absence of tubercle bacilli in the sputum on repeated examination practically excludes active pulmonary tuberculosis in the adult.

In one instance lipiodol was introduced in a patient in whom we had reason to suspect that a bronchiectatic condition rather than ulcerative tuberculosis existed in the right upper lobe. The patient, a man, aged 48, gave a history of hemorrhage for the preceding 17 years, recurring at irregular intervals, slight cough and expectoration. Since 1914 he had been hospitalized in Montefiore Hospital

and in its Country Sanatorium on 7 previous occasions, as well as in several other institutions. The physical findings revealed no clubbing of the fingers, no retraction of the apices, resonance on percussion, many râles and bronchocavernous breath sounds in both upper lobes, chiefly the right. At one time, in the Country Sanatorium, tubercle bacilli had been present in the sputum, but none was found on this occasion either by direct examination, with antiformin, or by guinea pig inoculation. The results of the lipiodol studies confirmed the clinical impression (Fig. 5). It is very likely that with more frequent use of lipiodol in the differential diagnosis of upper lobe disease, the condition of upper lobe bronchiectasis will be found as a symptomless condition in many more instances than we suspect. But when symptoms are present, bronchographic visualization will not give more information than can be obtained by physical and Roentgen examinations.

Tuberculosis and Apical Bronchiectasis. In a study of the post-mortem findings in approximately 750 patients who died of pulmonary tuberculosis and its complications, the coexistence of bronchiectasis was recorded in many instances, particularly in elderly individuals with long standing fibrotic disease. Unilateral upper lobe bronchiectasis involved more often the right lung, the site of the older tuberculous process in most patients. However, in the presence of active or even quiescent pulmonary tuberculosis an associated upper lobe bronchiectasis is of relatively minor clinical significance and for this reason such instances are not included in the present study. Our interest centers primarily in such instances of upper lobe bronchiectasis where the condition constitutes the dominant clinical feature of the disease. Recent experiences with 3 patients treated in the Tuberculosis Division of Montefiore Hospital have been particularly instructive, since they demonstrated the evolution of upper lobe bronchiectasis from a previously pathologically active pulmonary tuberculosis.

CASE 9.—A man (S. A.), aged 58, was admitted with a history of cough and expectoration of about 25 years' duration. On several occasions, he had blood streaked sputum and quite often paroxysms of dyspnea and cyanosis of the face and hands. The lung findings on physical and Roentgen examinations were characteristic of fibroid pulmonary tuberculosis with cavity formation in the left upper lobe. The sputum was positive. The patient left the hospital but returned on two subsequent occasions, 2 and 3 years later. At the time of the last admission, the physical and Roentgen findings revealed little change from those found previously. The sputum, however, did not contain tubercle bacilli on antiformin examination. The patient died. Autopsy revealed over both upper lobes large emphysematous blebs. In both upper lobes the bronchi were markedly dilated. There were no signs of active pulmonary tuberculosis.

CASE 10.—A man (L. P.), aged 49, was an inmate of the Tuberculosis Division for a period of 9 years. Aside from slight cough, expectoration and general debility, he had few symptoms. The physical and Roentgen findings were characteristic of fibrotic pulmonary tuberculosis involving chiefly the upper lobes. During the first 3 years of his stay the sputum contained tubercle bacilli on many occasions. During the remaining 6

years, the sputum was negative to antiformin. The patient died. Post-mortem examination revealed grossly a bronchiectatic condition in the left upper lobe and healed fibrotic tuberculosis. Microscopic examination revealed collapse induration of the lungs and anthracosis but no evidence of active pulmonary tuberculosis.

CASE 11.—A man (J. L.), aged 62, was in the Tuberculosis Division for a period of about 2 years. Clinically, he was suspected of having advanced pulmonary tuberculosis with cavity formation, although the sputum was negative for tubercle bacilli on 12 occasions. At necropsy, the patient had a healed fibrotic tuberculosis of the right upper lobe associated with extensive bronchiectasis. The right pleura revealed fibrous pleuritis and heteroplastic bone formation. The left pleura revealed calcified tubercles on the surface. This patient had a terminal miliary pulmonary tuberculosis that did not involve any other organ (Fig. 6).

Although active pulmonary tuberculosis was not demonstrable at necropsy in any of the 3 patients just described, one must presuppose from the presence at one time of tubercle bacilli in the sputum of 2 and the terminal miliary pulmonary tuberculosis in the 3d that a healed pulmonary tuberculosis was the cause of the upper lobe bronchiectasis revealed after necropsy. The end result was the same as in the 8 patients cited previously.

Summary. Bronchiectasis may involve and be confined to one or both upper lobes of the lungs. The clinical and Roentgen findings are in keeping with a diagnosis of chronic, fibro-ulcerative pulmonary tuberculosis with cavity formation. As a result, the patient sooner or later finds himself in an institution for the tuberculous where he is apt to remain for many years to be readmitted after discharge. Although, in the majority of instances the causative factor in the production of these upper lobe bronchiectatic dilatations is a healed pulmonary tuberculosis, it is the bronchiectatic condition that is clinically and morphologically the dominant process. In a lesser number of instances, a practically healed non-tuberculous chronic pneumonitis is the cause of the bronchiectasis.

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THE ASSOCIATION OF BENIGN AND MALIGNANT LESIONS OF THE ESOPHAGUS.*

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THE presence of two lesions in the esophagus points to a probable relationship of one to the other. If one is malignant, the association points to the possibility of the benign lesion being, directly or indirectly, the predisposing factor in the development of the malignant lesion. Conversely, however, the possibility of the carcinomatous lesion being the primary lesion, and the benign lesion a direct result of it, must be considered in a certain group of cases.

Fischer, in reviewing the factors which may have a predisposing influence in the production of carcinoma of the esophagus mentioned: (1) The site of scar formation; (2) injury from instrumentation; (3) chronic inflammatory processes, with the development of carcinoma in leukoplakia; (4) irritation by alcoholic beverages, and (5) chronic irritation from some extrinsic pressure as by aneurysm. Since the majority of carcinomas of the esophagus occur at the physiologic narrowings, he believes that pressure plays an important part. Ewing is of the opinion that anomalies of structure of the esophageal mucosa may be predisposing factors in the development of carcinoma but their exact importance has not been determined.

The probable relationship of the anatomic structure of the physiologic narrowings to the production of carcinoma led Benciolini to make a postmortem study of the esophagus of 44 men aged between 45 and 85 years. In 8 of these, he found at the physiologic narrowings, proliferative changes which included: (1) definite thickening of the mucosal epithelium; (2) round-celled infiltration in the submucosa, and (3) a proliferative reaction in the basal layer breaking through and disrupting the basal membrane. He does not call these changes precarcinomatous, but inflammatory reactions which in themselves are of no significance. Since they occur at the usual sites of formation of carcinoma they may be of some importance.

The relationship of cardiospasm to the production of carcinoma falls into the group entitled chronic inflammation of predisposing causes.⁹ The common occurrence of the new growth in the dilated portion of the esophagus is noteworthy. Fleiner, in a study of 40

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cases in which dilatation was present, found 3 in which the lesion had developed in the dilated portion of the esophagus. Comparing these to a group of cases of carcinoma of the esophagus without dilatation from cardiospasm, he computed that malignancy was likely to occur 25 times more often in the dilated esophagus. Wohlwill agreed that dilatation of the esophagus from cardiospasm predisposes to the development of carcinoma, but he thought that Fleiner's figures were too high. He reported 2 cases representative of this group; the patients were men aged 64 and 56. Cardiospasm had been present 17 and 15 years, respectively, before carcinoma developed. Wohlwill referred to a definitely neurotic background in the early symptoms of the first case, and added that if there is a functional basis for the production of cardiospasm and if cardiospasm is a predisposing factor in the production of carcinoma, then there is a functional disturbance playing a part in the development of malignant tumor. Moersch, in his report of cardiospasm among infants showed that probably there is no functional element concerned in true cardiospasm. Wohlwill felt that prompt elimination of the stagnation of food in the esophagus in such cases lessens the chance for the development of malignancy. Cade and Morenas, Giardina, and Rebattu and his associates, and others reported similar cases, the carcinoma developing in the dilated portion of the esophagus.

Neumann, in 1861, recorded the first case of carcinoma developing in a cicatrix. Cattell found an epithelioma in a stricture caused by lye in a man aged 66. Schirmer found a carcinoma beginning in an esophageal cicatrix, at necropsy on a man aged 62, whose history had not disclosed any trouble in the esophagus. Magnusson's patient, a man, aged 41, swallowed lye when 18 months old. Symptoms, apparently due to perforation of the esophagus into the right lung, developed 8 months prior to his death. At necropsy, a carcinoma was found between the physiologic narrowings of the esophagus and for this reason Magnusson felt justified in assuming that it originated in the scar tissue, extensive evidence of which was present in the remaining portion of the esophagus.

Fetzer reported the occurrence in a man, aged 54, of a benign stricture due to pleural adhesions causing kinking of the esophagus, and a second stricture caused by carcinoma.

Ewing stated that the physiologic narrowings form the site of diverticula. That these lesions may be associated with carcinoma has been shown. One of us (Vinson) reported 3 such cases. In the first case only was the carcinoma associated with the diverticulum; it was within the sac and extended to the posterior margin of the esophageal opening. In the second case, the carcinoma was in the middle third and the diverticulum was at the juncture of the pharynx and esophagus, whereas in the third case, the carcinoma occurred in the upper third and the diverticulum was slightly above the

cardia. In a case observed by Kaufmann the inner surface of the diverticulum was "lined with a white pultaceous cornified carcinoma," and in another case the lesion occurred at the entrance to the diverticulum. In another of Kaufmann's cases, a small oval isolated tumor was situated on the anterior wall of the esophagus. "The center of the pale gray red carcinoma showed a long depression of slate gray color which diminishing funnel-shaped, ended in an anthracotic chalky bronchial lymph node over the right bronchus."

The invasion of a fibrous polyp in the esophagus by an epithelioma is recorded by Targett. Schirmer observed an ulcerating carcinoma in close proximity to a lipomatous polyp near the cardiac end of the esophagus.

Multiple benign lesions associated with a malignant lesion are rare. Dean and Gregg reported the occurrence of tuberculosis and carcinoma of the esophagus of a patient with syphilis; the dysphagia improved following antisyphilitic treatment. Crile and Dinsmore saw a man, aged 55, who had a diverticulum, cardiospasm and a carcinoma of the esophagus.

Our search of the literature did not reveal any case of hysterical dysphagia in which carcinoma developed in the esophagus, although Cameron has stated that the type of mucous membrane seen in the esophagus in this condition is prone to undergo malignant degeneration. Suzman recently recorded a case in which carcinoma of the tongue and fauces was associated.

The cases presented here represent the association of carcinoma with 3 benign clinical entities in the esophagus: (1) cardiospasm, (2) cicatricial stricture resulting from the ingestion of lye, and (3) hysterical dysphagia.

Case Abstracts. CASE 1.—A man, aged 34, was examined at The Mayo Clinic April 30, 1925. He had had difficulty in swallowing for 8 years, at first mild, with a feeling of obstruction at the cardia on ingesting solid food. Later, the dysphagia became more marked and was especially pronounced when he attempted to swallow cold liquids. Complete closure of the esophagus had occurred on numerous occasions. These periods had lasted from 6 to 8 hours at a time. Occasionally he had regurgitated food after meals, but this had not occurred during the night. Slight pain in the epigastrium was noted at times. Treatment had consisted of the administration of antispasmodic drugs, with questionable benefit. He had lost 58 pounds.

General examination was essentially negative except for the marked emaciation. Roentgenoscopic examination of the esophagus revealed a smooth, obstructing lesion at the cardia with marked dilatation of the esophagus. May 3, 1925, the cardia was dilated with a hydrostatic dilator, and following this treatment, there was complete relief from dysphagia although further roentgenographic study of the esophagus showed that there was slight lagging of the barium meal at the cardia.

During the next year, the patient gained 40 pounds, but returned to the clinic the latter part of June, 1926, because of slight dysphagia. At that time, a No. 45 French sound was passed through the cardia without obstruc-

tion. The patient did not seem to be suffering from sufficient dysphagia to necessitate further hydrostatic dilatation. No further trouble was experienced until December, 1931, when the patient began to notice progressive dysphagia. When he returned for examination March 25, 1932, there had been a loss of strength and 20 pounds weight. Roentgenograms revealed the presence of an irregular filling defect in the lower portion of the esophagus that extended to within 2.5 cm. of the cardia. Esophagoscopy was done, and a large ulcerating lesion, without obstruction, was found on the left posterior wall of the esophagus. This lack of obstruction was due apparently to the fact that the esophagus was dilated as a result of the previous cardiospasm. A section of tissue removed for microscopic study showed it to be papillary squamous-cell epithelioma, graded 2.

The general condition of the patient was good, and it was hoped that because of this and redundant esophageal tissue, the lesion could be removed at operation. However, on exploration, the growth was found to have extended posteriorly, with fixation around the aorta and spine. The condition was considered inoperable, but deep Roentgen therapy was instituted, and at the last report, December 26, 1932, the patient was still living.

This case differs from most of those reported by other investigators, as the region of malignant disease was sufficiently extensive to produce obstruction in the esophagus and permit an antemortem diagnosis.

CASE 2.—A woman, aged 38, came to the clinic for examination January 24, 1923. At the age of 18 months she had swallowed a solution of lye, and following this an esophageal stricture had developed. For 6 years, she had experienced more or less trouble in swallowing, but from the age of 8 to 32, the symptoms of obstruction had been minimal. Dilatations were made when she was 15, and following these, there was a pulmonary complication that suggested the presence of an esophagobronchial fistula. Two years before she came to the clinic for treatment, the obstruction had become marked, and she had lost 40 pounds. Dilatations had been carried out with moderate benefit, but after each there would be complete closure of the esophagus for about 12 hours.

Examination revealed a stricture in the esophagus, about 31 cm. from the incisor teeth. Its appearance on roentgenoscopic examination and at esophagoscopy seemed to indicate that the lesion was benign. For 10 weeks, the stenosis was gradually dilated until a No. 40 French sound could be passed without difficulty. The dysphagia became less marked and the patient was permitted to return home. Four weeks following the last dilatation she experienced a sense of strangulation on swallowing liquids and fever began to develop. Examination disclosed a fistula between the esophagus and left bronchus. It was concluded that this was the result of the dilatation of scar tissue which had produced partial healing after perforation that had occurred 23 years before. Gastrostomy was performed May 23, 1923. The patient died September 24, 1924.

At autopsy, it was found that the esophagus was densely scarred and the periesophageal tissues were infiltrated, but the entire process seemed inflammatory. Microscopic section of the tissue revealed that it was a squamous-cell epithelioma.

Numerous cases of this type have come under observation. It is likely that the scar tissue produced in the esophagus by the swallowing of lye is a predisposing factor in the developing of malignant degeneration. However, it is remarkable that, in our experience,

a malignant lesion in the esophagus has not followed a benign stricture from any other cause than lye.

CASE 3.—A woman, aged 39, came to the clinic July 26, 1929. Nine years previously she had noted mild choking sensations, but this had been relieved by tonsillectomy. One year before admission, she began to have trouble in swallowing especially when attempting to eat solid foods. There had been a slight loss in weight, and rather marked anemia had developed.

At examination, the obstruction was noted high in the esophagus. The concentration of hemoglobin was 42 per cent (Dare), and erythrocytes numbered 4,250,000 per c.mm. All the upper teeth were absent, and few remained below. There was a full denture above and a partial plate below. The corners of the lips were cracked and the tongue was smooth. The spleen could not be palpated. Examination of the esophagus revealed nothing abnormal, and following the passage of a No. 41 French olive into the stomach, the patient was relieved completely from dysphagia. She remained well for 2½ years.

In January, 1932, dysphagia returned and was associated with soreness of the throat, but when the patient was again examined in September, 1932, her general condition seemed better than at the time of the first examination. The concentration of hemoglobin was 85 per cent. Examination of the esophagus revealed an ulcerating lesion at the introitus, and tissue removed for microscopic study was reported to be squamous-cell epithelioma, graded 3.

In the observation of patients suffering from carcinoma of the esophagus one is impressed with the long history of dysphagia in a small group of cases. In a few cases, we have felt that functional dysphagia had been present for many years before carcinoma had appeared, and in several cases of definite hysterical dysphagia, malignant degeneration occurred a few years subsequently.

Summary. The literature relating to benign lesions of the esophagus, which seem to increase the predisposition of the esophageal mucosa to the development of carcinoma, is reviewed. Three cases, cardiospasm, stricture caused by lye and hysterical dysphagia, respectively, each associated with the development of carcinoma of the esophagus, are recorded. It is believed that the case of hysterical dysphagia is the first reported in which carcinoma of the esophagus has developed.

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THE DIAGNOSIS OF CARCINOMA OF THE COLON.

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THE subject of carcinoma of the large bowel has been receiving much attention in the past few years. The signs and symptoms of this disease, as described in the textbooks, are so numerous as to be confusing. It would seem that any abdominal complaint might indicate new growth. In order to attempt to clarify the subject, or at least to establish the signs and symptoms of chief significance, it was determined to review a typical group of such cases. An analysis has been made of 53 carcinomas of the colon admitted to this Division in the 10-year period, January 1, 1922, to December 31, 1931.

These cases were grouped as follows:

<i>Location.</i>		<i>Age Incidence.</i>	
Cecum	7	Under 20	1
Ascending colon	6	20 to 29	2
Hepatic flexure	6	30 to 39	3
Transverse colon	5	40 to 49	9
Splenic flexure	7	50 to 59	14
Descending colon	4	60 to 69	14
Sigmoid colon	18	70 to 79	9
	—	80 on	1
	53		—
			53

Symptoms. The average duration of symptoms on first observation has been found to be 8 months. The usual story was that of an ailment mild at first, gradually becoming more severe, and finally forcing the patient to consult a physician. Frequently the diagnosis failed to be made by several physicians before some careful man

discovered the disease. In such cases the outstanding complaints were abdominal discomfort or pain and weight loss.

1. The abdominal discomfort at first was apt to be vague and diffuse, giving rise later to a dull pain that was not sufficient to interfere with work. The patients frequently believed that an "indigestion" was present, and related a history of use of cathartics and dietary restriction. Later, if the neoplasm involved the right half of the colon, pain was referred to the right lower or upper quadrants, usually the lower. If the left half was involved, the pain was referred to the umbilical region or below, rarely to the left colonic region. A few of our patients had continuous discomfort; the great majority had periodic attacks of pain. As the obstruction increased, attacks of colic became more frequent and pronounced. In the severe attacks of colic, the pain was usually referred to the same site as when the pain was dull. We were unable to elicit any history of abdominal discomfort in 4 cases. Two of these had cancer of the ascending colon, and 2 of the sigmoid colon.

2. Weight loss was the second prominent symptom. At least 10 pounds, and usually more, were lost, while 1 case had lost 80 pounds. Five patients with annular carcinoma of the left colon had no loss of weight.

3. Constipation is regarded as an outstanding feature of carcinoma of the large bowel. It is more pronounced in lesions of the left half than of the right half of the colon. Much to my surprise, *one-third* of the cases observed never complained of constipation. How much this may have been due to the use of mineral oil and other regulators of the bowel, it is difficult to discover. Certainly the wide use of mineral oil has been a large factor in helping to soften feces so that obstipation is less frequently observed. Of the two-thirds that complained of constipation, we noted an almost uniform report that the constipation gradually became more and more severe. Such patients often were bothered by borborygmus, increased flatus, and belching.

4. Diarrhea in growths above the rectum is an almost negligible symptom. The conventional idea is that the typical case reported alternating periods of constipation and diarrhea. We had only 3 such cases.

5. Blood in the stool was not reported for any tumor situated between the cecum and the splenic flexure in cases of cancer. From this point to the rectum there were many reports of blood in the stool. Of the 18 carcinomas of the sigmoid, 7 reported blood. Occult blood was not searched for in a sufficient number of cases to warrant conclusions; I am inclined to believe that a careful search after a sufficient period on a meat-free diet might be helpful in diagnosis.

6. Mucus in the stool was rarely mentioned by the patient, yet in a few cases there was marked evidence of both mucus and blood.

This was likely to be the case in cancers of the lower sigmoid, where the anatomic differentiation between sigmoid and rectum becomes difficult.

7. The tumor mass was felt only once by rectum. This was in a case in which the growth prolapsed from the sigmoid into the rectum. At operation its location was found to be well up in the middle sigmoid. Above the limit of sigmoidoscopic examination palpable abdominal tumor may be found. In 38 cases where the question of a mass was considered in the history, there were 25 in which a tumor could be palpated and 13 in which no tumor could be felt.

8. Secondary anemia was present to a moderate degree in many cases, and to a marked degree in a few. The polypoid types of growth, rather than the annular cancers, seemed to be associated with the more marked secondary anemias. Their surfaces erode more readily and bleed more freely into the intestine.

9. Obstruction may be chronic or acute. The chronic partial obstruction arises from *annular* or *polypoid* growth in the colon. In the *annular* type there develops a submucous growth in which there is much fibrous tissue. Usually there is but little ulceration. In time the lumen becomes narrow because of contracture of the scar tissue. In the *polypoid* type the tumor grows into the lumen from a part of the wall. This form is often accompanied by necrosis of the growth followed by ulceration of the mucous membrane. Obstruction, in its early stage, may give rise to borborygmus and other symptoms of colonic irritability. Of our cases 85 per cent gave indications of some chronic obstruction. The degree of obstructive symptoms is largely influenced by the segment of bowel involved. In the right half of the colon the contents are liquid, and they find but little difficulty in going through a stenosed lumen. In the left half the contents lose their fluid character to become formed, so that much less stenosis is required to cause obstructive symptoms.

Acute obstruction arises when the lumen becomes suddenly occluded or when the tumor causes an intussusception. In the annular growth acute ileus results when the narrow lumen becomes plugged. The polypoid growth causes acute ileus when ulceration, acute inflammation and edema occur.

In our series 1 case of acute obstruction, due to intussusception, occurred in carcinoma of the cecum. Between the cecum and splenic flexure no other case of obstruction occurred. *One-third* of the patients suffering from cancer of the bowel below this point required emergency surgery because of acute obstruction.

Roentgen ray study of the gastro-intestinal tract has become increasingly useful in diagnosis. In the study of tumors of the large bowel one depends on the administration of barium by mouth and by anus. Of the two methods, the barium enema is the more important. The diagnosis of growth in the bowel is dependent on demonstration of infiltration of the gut wall, with narrowing of its lumen.

In early cases, with carcinoma above the rectosigmoid, barium may fill out the lumen above and below the growth in such a manner as to fail to show the lesion. This error may be avoided by taking a sufficient number of films from different angles. But more important still is the necessity for fluoroscopic examination of the barium enema. With this method the barium may be seen to enter and fill out the bowel as it proceeds. One thus has a splendid opportunity to see any defect or deformity in the bowel wall. Of our 40 cases with reported Roentgen ray findings, 31 had positive diagnosis, 4 were questionable, and 5 were reported negative.

Differential Diagnosis. 1. CHRONIC DIVERTICULITIS. One source of error in Roentgen diagnosis should be emphasized. Such an error occurs when new growth of the colon is diagnosed as chronic diverticulitis. As previously stated, we are dependent on infiltration of the gut wall with narrowing of the lumen for our diagnosis of cancer. In diverticulitis there may occur a single diverticulum, associated with a chronic inflammation, that simulates new growth. In this condition it is practically impossible to make a pre-operative differential diagnosis. At operation, the problem is still great. It has been my fortune to assist at several major operations on the colon where the lesions were thought to be malignant but which subsequently were proven to be the result of inflammation associated with diverticulitis. It is a most difficult problem. Eggers¹ recently has emphasized this fact, again, by reporting 2 cases of diverticulitis that had carcinoma of the bowel associated with them. He does not believe that diverticulitis is a precancerous disease. He reports these cases as showing the presence of cancer in areas in which the Roentgen ray had demonstrated chronic diverticulitis. The clue to the correct diagnosis must be found elsewhere. "So far as can be made out from statistics, bleeding associated with diverticulitis of the colon alone occurs in 5 per cent of these cases. It is evident, therefore, that great care must be taken to avoid overlooking carcinoma of the colon when there has been bleeding and a diagnosis of diverticulitis has been made by Roentgen ray. In my own cases, if I had depended on the Roentgen ray diagnosis of diverticulitis with bleeding, an error would have been made in 75 per cent of the cases, while if operation had been carried out in all cases, the operation would have been an error in but 25 per cent. It is exceedingly dangerous to make a diagnosis of diverticulitis of the colon even with the aid of the Roentgen ray when there is bleeding associated with it."²

2. CHRONIC ULCERATIVE COLITIS. In illustration of the diagnostic problem involved in differentiating between this condition and cancer, the following case is cited:

Case Abstract (B30820).—B. A., aged 27, female, 3 years before admission, had a severe attack of abdominal colic. This was relieved by flatus and loose stool, with blood and mucus. Gastro-intestinal series subse-

quently were reported negative. For 2 years the patient enjoyed good health and gained in weight. She then began to have similar attacks although varying in severity. She went to a rectal specialist at that time. He ordered a barium enema and a gastro-intestinal Roentgen ray examination. The report was negative for disease. Symptoms persisted, with freedom from attacks of 1 to 3 months' duration. The later attacks were quite severe, with lower abdominal pain, nausea and vomiting, and no relief afforded by enemas or irrigations. Suddenly some flatus would be expelled, and feces, blood and mucus would follow with relief of symptoms until the next attack. Finally the patient changed doctors and the third Roentgen ray examination demonstrated a growth in the splenic flexure. This diagnosis was confirmed at operation. This patient was interesting because of her age, the duration of symptoms, the complete failure of two Roentgen ray examinations, and the fact that the colon specialist was content to treat her for almost a year as a case of ulcerative colitis.

3. PERITONEAL ABSCESS.

CASE 2 (B21404).—S. E., aged 40, female, had been sick for 2 weeks with pain in the left lower quadrant of the abdomen. Examination showed an ill-defined mass in the pelvis, and tenderness in the left vaginal fornix. There had been no constipation and no suggestion of intestinal disease. White blood cells, 11,000 and polymorphonuclears 80 per cent. Operation for drainage of a pelvic abscess revealed carcinoma of the sigmoid with localized perforation.

4. OVARIAN CYST. I have assisted at three gynecologic operations (not reported in this series) at which, the pre-operative diagnosis being left ovarian cyst, carcinomas of the bowel were found. At times it is admittedly difficult to differentiate between these conditions, but the possibility of cancer of the sigmoid must be borne in mind and a more frequent use made of the barium enema with Roentgen ray study to exclude it.

5. HYPERPLASTIC TUBERCULOSIS. Hyperplastic tuberculosis is usually confined to the cecum and ascending colon. It bears a striking resemblance to malignancy in its clinical history and laboratory findings. The patient has abdominal pain, and loss of weight, but as a rule its course is slower and more insidious. A 3-year history of illness is usual in this disease, as compared with our average 8 months in malignancy. Both produce secondary anemia, and both may give constipation and partial obstruction. The average age of incidence is lower in tuberculosis. The Roentgen ray differentiation may be exceedingly difficult. The presence of tuberculosis elsewhere may be helpful to the diagnosis. Even at operation the distinction may be difficult.

6. GRANULOMA. Granuloma of the cecum is a pathologic entity that is met now and then. Its cause is not well understood, and its differential diagnosis from carcinoma and hyperplastic tuberculosis is quite difficult. At operation one meets thickened gut walls often with narrowing at one area and thickening and dilatation proximal. The mesenteric lymph nodes may or may not be enlarged. In the single case in my personal experience, I performed a resection

under the impression that I was dealing with a tuberculosis of the cecum. Others have performed similar operations mistaking the condition for carcinoma of the cecum.

Summary. 1. Carcinoma of the colon is a disease of middle and late life.

2. Chief symptoms are abdominal discomfort and loss of weight.

3. Partial obstruction with its characteristic symptoms is usually present.

4. Acute ileus is an important symptom in malignancy of the left side of the colon.

5. Roentgen ray examination should be helpful when both films and fluoroscope are used.

6. The disease must be differentiated from: (a) chronic diverticulitis; (b) chronic ulcerative colitis; (c) peritoneal abscess; (d) pelvic and ovarian disease; (e) hyperplastic tuberculosis; (f) granuloma.

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THE CHOLESTEROL CONTENT OF THE PLASMA IN CHRONIC NEPHRITIS AND RETENTION UREMIA.*

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CHAUFFARD, Laroche and Grigaut¹ state that the blood cholesterol in nephritic subjects without uremia is usually high, but with increasing nitrogen retention it tends to fall as if there were an inverse relation between urea and cholesterol. Schmidt² shows that hypercholesterolemia frequently occurs in patients with Bright's disease, high blood pressure and related conditions; when there is marked renal insufficiency, the cholesterol content of the blood falls and may even become subnormal; he stresses the prognostic significance of his data. Henes³ declares that all cases of chronic nephritis terminating fatally in coma show a hypocholesterolemia. Epstein and Rothschild⁴ describe the high blood cholesterol of chronic "parenchymatous" nephritis which, they show, falls

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with the onset of uremia. Campbell⁵ thinks that the cholesterol values are high in chronic "parenchymatous" nephritis, less so in chronic "interstitial" nephritis, and declares that in the latter condition a fall in the blood cholesterol occurs if uremia begins. Lesné, Zizine and Sylvestre⁶ note a hypocholesterolemia in cases of severe acute nephritis. Fleming⁷ calls a falling blood cholesterol a poor prognostic sign portending uremia, irrespective of the presence or absence of edema.

In contrast with the literature cited above, Bennett, Davies and Dodds⁸ speak of the blood cholesterol being normal usually in nephritic patients where uremic and cardiovascular changes dominate the picture, as compared with the high cholesterol reading in "nephrosis."

Still further contrast is afforded by the analyses of Maxwell,³ indicating that a persistently elevated plasma cholesterol occurring in patients who had been edema-free for a long period is often associated with the early onset of uremia. Yet (according to Maxwell), the cholesterol is normal or low in uremia.

Material and Methods. In the present paper the data of 24 cases of chronic Bright's disease are submitted. Only the significant results are tabulated but, in all, over 200 simultaneous determinations of the whole blood urea nitrogen and the plasma cholesterol were made. The majority of these cases were studied for 2 or more years, alternately in the wards of the New York Post-Graduate Hospital and in private practice.

Prior to 1928, the whole blood urea nitrogen was determined according to the method of Myers;¹⁰ since then by the gasometric urease method of Van Slyke.¹¹ The plasma cholesterol was determined chiefly by Sackett's method¹² modified since 1931 by the temperature control procedure used in this laboratory;¹³ rarely by the method of Myers and Wardell.¹⁴

The numerous analyses in the literature on the cholesterol content of the blood indicate that a plasma cholesterol from 160 to 230 mg. per cent may be considered as "normal." We have often observed a plasma cholesterol (in single blood studies) as high as 250 mg. per cent in "normal" fasting subjects (laboratory workers, interns, etc.). For these reasons we have considered a plasma cholesterol below 160 mg. per cent as subnormal (hypocholesterolemia), from 160 to 230 mg. per cent as the average normal range, from 230 to 250 mg. per cent as suggestive of hypercholesterolemia but still within the normal limits, and above 250 mg. per cent as definitely elevated (hypercholesterolemia).

Analysis of Data. Table 1 comprises the data on the simultaneous determinations of the whole blood urea nitrogen and the plasma cholesterol in 9 patients who died in uremic coma. The terminal urea nitrogen is high—over 100 mg. per cent in 8 of the 9 cases. The plasma cholesterol, terminally, is low or average normal (as

low as 83 mg. per cent in Case 3) in all cases except Case 9. In this patient the last cholesterol determination (250 mg. per cent) was made 2 days before death. There is a reasonable likelihood that the cholesterol on the day of death was lower than 250 mg. per cent; for example, we may cite Case 8, in which the cholesterol fell from 217 to 178 mg. per cent in 24 hours before death occurred in uremia.

From a study of Table 1 (and a comparison with Table 3) we observe that the finding of a low plasma cholesterol in a patient with marked nitrogen retention is of more prognostic value as to predicting death in uremia than the level of the blood urea nitrogen. For example, of the patients dying in uremic coma manifesting a low plasma cholesterol, Case 2 had a terminal urea nitrogen of 100 mg. per cent, Case 4, 86 mg., and Case 9, 119 mg. Yet, in Table 3 we have recorded patients with a high plasma cholesterol who did well and were relieved of uremic symptoms although the blood urea nitrogen was as high or higher than the 3 fatal cases cited. Moreover, in any individual case the same fact is often observed. We have seen patients feeling well and going about their work for months with a blood urea nitrogen almost as high as (rarely higher than) that recorded at the time of death. At the time when they were ambulatory the plasma cholesterol was high; terminally the cholesterol was low.

There appears to be no close relation between the height of the plasma cholesterol and the degree of edema manifested by these patients. In Case 1 there was no appreciable difference in the amount of edema when the cholesterol ranged from 477 to 667 mg. per cent on the one hand, as compared to the edema noted when the cholesterol ranged from 200 to 172 mg. per cent, on the other. In Case 9 fluctuations of the plasma cholesterol from 416 to 250 mg. per cent were accompanied by no parallel variations in edema. A cholesterol of 285 mg. per cent in Case 4 is accompanied by no edema, though marked edema is associated with a cholesterol of 172 mg. per cent in Case 1 and 238 in Case 9.

Table 2 shows 3 cases of chronic Bright's disease dying of intercurrent infection—2 of pneumonia and 1 of erysipelas. At the time of death the plasma cholesterol was over 325 mg. per cent in each case. This is in distinct contrast with the low value for cholesterol observed in 9 cases dying in uremia. Thus, while a high plasma cholesterol enables us to reassure the patient that uremia is not imminent, it does not preclude the possibility of death from causes other than uremia.

As in Table 1, so in this group, no constant relation is observed between the height of the plasma cholesterol and the degree of edema. Case 11 had a plasma cholesterol of 326 mg. per cent and practically no edema; the cholesterol of Case 10 was not significantly higher (385 mg. per cent) but the patient was markedly edematous.

TABLE 1.—SIMULTANEOUS DETERMINATIONS OF BLOOD UREA NITROGEN AND PLASMA CHOLESTEROL IN 9 PATIENTS DYING IN UREMIC COMA FOLLOWING RENAL INSUFFICIENCY OF PRIMARY OR SECONDARY CONTRACTED KIDNEY.

Case No.	Age and sex.	Date.	Whole blood urea N ₂ , mg. %.	Plasma cholesterol, mg. %.	Plasma carbon dioxide combining power, vol. %.	Blood pressure.	Albuminuria.	Edema.	Total serum proteins, gm. %.	Blood count.		Remarks.
										Hb., %.	R.B.C., millions.	
1	23, M	12/22/30	18	667	...	168/98	++	++	4.2	66	3.79	Patient discharged after recovering from uremic symptoms.
		5/28/31	49	555	...	174/102	++	++	5.4	
		4/18/32	84	477	++	++	
		5/31/32	108	436	++	++	...	52	3.12	
		6/14/32	93	360	++	++	
2	46, M	9/ 8/32	111	239	++	++	5.5	Died in uremia, 10/3/32.
		9/29/32	153	264	++	++	5.6	69	4.23	
		9/30/32	164	200	25.8	240/144	++	++	6.8	
		10/ 2/32	171	172	++	++	6.0	105	4.61	
		1/31/30	17	158	++	++	6.2	
3	28, M	4/15/32	58	242	++	++	6.5	Died in uremia.
		4/18/32	85	245	++	++	5.9	
		4/21/32	98	208	++	++	
		4/23/32	93	199	++	++	
		4/26/32	95	174	++	++	
4	39, F	4/30/32	100	150	++	++	Note extremely low cholesterol; died in uremia.
		9/ 6/27	20	184	...	230/130	++	++	4.7	70	3.52	
		1/10/28	115	112	25.8	172/88	++	++	
		1/16/28	238	83	++	++	
		12/14/31	86	250	...	230/140	++	++	...	40	2.06	
5	38, M	12/15/31	135	285	++	++	Died in uremia. Transfusion.
		12/28/31	87	151	41.9	...	++	++	...	26	1.81	
		1/ 7/32	106	133	47.5	...	++	++	
		1/14/32	87	129	++	++	
		1/20/32	86	141	++	++	
6	42, M	5/ 7/25	47	240	...	182/118	++	++	Died in uremia.
		7/13/26	64	120	++	++	
		10/ 2/26	130	182	++	++	
		10/18/26	124	164	++	++	
		10/25/26	184	149	++	++	
7	40, M	3/13/31	110	180	33.4	166/86	++	++	...	41	2.38	Died in uremia.
		3/17/31	124	144	30.5	238/132	++	++	
		3/20/31	153	165	26.8	210/166	++	++	
		10/13/24	151	155	34.3	194/112	++	++	6.5	
		10/15/24	345	140	39.0	184/110	++	++	
8	23, M	4/24/31	218	260	26.8	178/110	++	++	Died in uremia.
		4/25/31	242	203	...	178/130	++	++	
		4/27/31	264	167	++	++	...	45	2.32	
		4/28/31	268	217	++	++	
		4/29/31	276	178	++	++	
9	36, M	3/28/31	36	238	...	140/92	++	++	Uremic acidosis; last cholesterol 2 days before death.
		4/16/31	28	416	++	++	
		4/28/31	39	369	++	++	
		7/ 1/31	117	250	8.0	...	++	++	7.1	
		7/ 3/31	119	...	7.0	...	++	++	

The terminal blood urea nitrogen is above 80 mg. per cent in every case. A fall of the plasma cholesterol below 180 mg. per cent is observed in every case, except 1, at the time of death.

TABLE 2.—SIMULTANEOUS DETERMINATIONS OF BLOOD UREA NITROGEN AND PLASMA CHOLESTEROL IN 3 PATIENTS WITH CHRONIC DIFFUSE GLOMERULAR NEPHRITIS WHO DIED OF CAUSES OTHER THAN UREMIA.

Case No.	Age and sex.	Date.	Whole blood urea N ₂ , mg. %.	Plasma cholesterol, mg. %.	Blood pressure.	Albuminuria.	Edema.	Total serum proteins, gm. %.	Blood count.		Remarks.
									Hb., %.	R.B.C., millions.	
10	32, F	2/5/29	18	469	148/96	++++	++++	..	61	3.50	Transfusion.
		6/19/29	28	667	...	++++	++++	..	52	2.80	
		9/19/29	23	588	...	++++	++++	
		9/27/29	72	554	...	++++	++++	
		10/ 3/29	140	460	...	++++	++++	..	70	3.74	
		10/ 9/29	52	370	...	++++	++++	Died of pneumonia.
		10/22/29	69	459	...	++++	++++	
		11/ 2/29	52	385	...	++++	++++	
11	30, M	1/ 3/27	41	279	172/108	++++	±	6.4	55	2.90	Died of pneumonia.
		4/29/27	27	242	...	+++	±	..	48	2.70	
		8/ 5/27	35	326	240/142	...	±	..	45	3.01	
12	21, M	11/27/24	41	173	140/100	++	++++	3.5	Hematuria.
		12/ 2/24	36	231	128/94	++	++++	Erysipelas of the lower extremities and back began 3/27/25. Died of erysipelas.
		12/29/24	22	294	132/90	++++	++++	3.0	
		1/21/25	32	200	138/92	++++	++++	3.6	
		3/16/25	20	320	...	++++	++++	..	42	2.40	
		3/30/25	30	352	...	++++	++++	

The plasma cholesterol is above 300 mg. per cent in every case at the time of death.

Table 3 details a series of observations on the simultaneous whole blood urea nitrogen and the plasma cholesterol in 12 patients with chronic Bright's disease. These individuals, despite marked, moderate or slight elevations of the urea nitrogen, are alive and feeling well and, in most instances, carrying on their usual business or professional activities. The plasma cholesterol is over 200 mg. per cent in 10 of the 12 patients. This is in distinct contrast to the cases in Table 1.

As has already been pointed out, in 3 instances among the cases in Table 3 the blood urea nitrogen was actually as high or higher than that of some of the fatal cases. Nevertheless, these patients recovered from their pre-uremic symptoms and were able to return to work; the cholesterol at the time they manifested a high blood urea nitrogen, headache, vomiting, etc., was over 200 mg. per cent. (Of the 12 cases listed in Table 3, all but 1, Case 13, are alive today. Case 13, male, aged 19 years, lived 4 months after the last recorded date; he died elsewhere and we are unable to furnish the terminal data.)

It is significant that the patients who are doing well have a high plasma cholesterol although there is little edema. This is a group conspicuous for its elevated cholesterol, yet it is also characterized by little or no edema.

TABLE 3.—SIMULTANEOUS DETERMINATIONS OF BLOOD UREA NITROGEN AND PLASMA CHOLESTEROL IN 12 PATIENTS WITH CHRONIC DIFFUSE GLOMERULAR NEPHRITIS ALIVE AND DOING WELL.

Case No.	Age and sex.	Date.	Whole blood urea N ₂ , mg. %.	Plasma cholesterol, mg. %.	Plasma carbon dioxide combining power, vol. %.	Blood pressure.	Albuminuria.	Edema.	Total serum proteins, gm. %.	Blood count.		Remarks.
										Hb., %.	R. B. C., millions.	
13	19, M	12/31/31	56	234	...	158/110	++	=	...	59	3.90	Transfusion.
14	26, M	6/10/32	113	212	++	=	6.4	72	4.20	Discharged feeling fairly well.
		1/ 8/32	89	243	++	0	Discharged; headache and vomiting relieved; feeling better.
		1/10/32	95	186	...	150/102	++	0	Discharged; feeling better.
		1/13/32	97	206	++	0	Discharged; feeling better.
15	17, M	6/13/32	96	227	++	++	6.4	52	2.49	Discharged; feeling better.
16	30, F	6/28/32	87	280	++	++	Hematuria.
		7/ 9/32	(N.P.N. 120)	335	++	++	Signed release; feeling fairly well.
		3/10/32	63	403	27.1	212/114	++	+	...	34	2.26	Vomiting; headache.
		3/17/32	61	291	38.1	188/120	++	+	...	40	2.09	Feeling fairly well.
17	19, M	3/25/32	63	248	...	170/100	++	+	...	32	1.50	Living and at work 6 months after this determination.
		4/19/32	75	280	...	180/115	++	+	4.6	Feeling well.
		4/ 1/32	47	320	...	210/140	++	=	Note low cholesterol but no elevation of urea nitrogen.
		5/ 2/32	59	337	++	=	Discharged; improved; working.
18	27, M	6/ 3/32	59	297	++	=	Feeling very well.
		7/ 8/32	56	256	...	149/116	++	=	...	76	4.00	Discharged; improved.
		9/29/30	39	244	...	154/102	++	=	...	72	3.40	Sudden drop in cholesterol; feeling badly.
		2/12/31	55	483	...	146/96	++	=	...	60	3.27	Discharged; feeling better.
19	46, M	12/15/31	53	470	...	146/96	++	=	...	60	3.28	Feeling well.
		1/22/32	51	350	...	150/104	++	=	...	56	3.10	Note low cholesterol but no elevation of urea nitrogen.
		4/14/32	44	174	++	0	...	52	2.34	Discharged; improved; working.
		4/ 8/32	31	338	38.1	162/92	++	++	6.2	Feeling very well.
20	44, M	5/ 7/32	53	507	++	++	...	82	4.20	Feeling very badly.
		5/31/32	43	375	++	++	6.9	75	..	Discharged; improved.
		10/ 3/32	23	372	57.9	130/90	++	++	...	87	5.04	Feeling very well.
		4/24/26	16	201	...	134/96	++	++	...	75	4.30	Feeling very well.
21	50, M	7/ 3/26	24	150	++	++	...	84	4.47	Feeling very well.
		6/ 6/29	19	300	...	146/96	++	=	Feeling very badly.
		7/13/32	24	300	...	184/106	++	=	5.5	Discharged; improved.
		7/26/32	20	320	...	154/96	++	=	Sudden drop in cholesterol; feeling badly.
22	24, M	10/ 5/32	23	257	...	202/132	++	++	Discharged; feeling better.
		5/ 5/28	22	179	++	++	Doing well.
		5/16/28	18	226	++	++	2.5	Feeling very well.
		5/25/28	29	161	++	++	Feeling very well.
23	19, F	6/ 6/28	26	300	43.8	...	++	++	Feeling very well.
		2/16/32	39	295	++	++	Feeling very well.
		5/11/32	49	212	++	++	Feeling very well.
		5/17/32	49	221	...	178/120	++	++	Feeling very well.
24	61, M	5/27/26	30	240	...	176/100	++	++	Feeling very well.
		7/28/26	34	133	...	141/70	++	++	Feeling very well.
		9/16/26	20	240	...	172/76	++	++	Feeling very well.
		1/ 4/27	32	166	...	166/72	++	++	Feeling very well.

Irrespective of the height attained by the blood urea nitrogen (in some instances higher than that found in the fatal cases shown in Table 1) these patients did well and occasionally recovered from their uremic symptoms. The plasma cholesterol, with few exceptions, was 200 mg. per cent or above.

TABLE 4.—THE CHOLESTEROL CONTENT OF THE PLASMA IN CACHECTIC AND ANEMIC NON-NEPHRITIC PATIENTS (TUBERCULOSIS, AMYLOIDOSIS, CARCINOMA, APLASTIC ANEMIA AND SUBACUTE BACTERIAL ENDOCARDITIS).

Case No.	Age, yrs.	Diagnosis.	Whole blood N.P.N., mg. per 100 cc.	Plasma cholesterol, mg. per 100 cc.	Remarks.
1	33	Bilateral caseous pneumonic tuberculosis	27	134	Duration of 4 yrs.
2	20	Bilateral caseous pneumonic tuberculosis; amyloidosis	..	133	Duration of 1 yr.
3	31	Tuberculous peritonitis	..	113	Duration of 2 yrs.
4	37	Unilateral caseous pneumonic tuberculosis; empyema	31	132	Duration of 3 yrs.
5	28	Bilateral caseous pneumonic tuberculosis	..	Trace	Duration of $\frac{1}{2}$ yr.
6	28	Unilateral caseous pneumonic tuberculosis; empyema.	27	127	Duration of 7 yrs.
7	32	Bilateral caseous pneumonic tuberculosis; amyloidosis	30	127	Duration of $\frac{1}{2}$ yr.
8	49	Adenocarcinoma of esophagus; marked secondary anemia	30	113	Hb., 17%; eryth., 1,790,000; corp. vol., 14.5%.
9	55	Aplastic anemia (Roentgen ray)	29	109	Hb., 26%; eryth., 1,400,000; lcts., 1900.
10	27	Subacute bacterial endocarditis; right upper and middle lobe pneumonia; right empyema; fibrinopurulent pericarditis	49	136	Hb., 63%; eryth., 3,090,000.

The marked hypocholesterolemia observed in non-nephritic patients with cachexia and anemia is evident from the cases cited above. In 1 instance (Case 5) the plasma cholesterol was so low that accurate colorimetric estimation was not possible.

Cases 20, 22 and 24 illustrate a point which deserves emphasis. At times in the course of the disease a low plasma cholesterol was reached (150, 161 and 133 mg. per cent, respectively). Yet, since this occurred when there was practically no nitrogen retention, no uremic symptoms were observed. One patient (Case 22) felt poorly when the cholesterol fell from 226 to 161 mg. per cent within 9 days, although the blood urea nitrogen increased from 18 to 29 mg. per cent. It would thus appear that *a low plasma cholesterol is prognostic of death in uremia in a case of Bright's disease only at a time when the blood urea is elevated*; at other times the cholesterol may fall without the threat of a fatal outcome.

Discussion. The general facts that a low or subnormal plasma cholesterol is associated with impending death in uremia in patients with advanced Bright's disease, while a high plasma cholesterol indicates a favorable outcome so far as uremia is concerned, have been discussed in the analyses of the 3 tables presented. There remains the consideration of the possible cause for the decreased plasma cholesterol observed in cases with a poor outcome.

Three main approaches suggest themselves: I. The existence of an inverse relation between the plasma cholesterol and some other blood constituent: (a) urea, (b) plasma proteins. II. The effect of cachexia. III. The effect of anemia.

I. (a) Since a low plasma cholesterol is observed in uremic subjects with nitrogen retention, it may be inferred that as one constituent (urea) rises, the other falls. This view has been expressed by Chauffard, Laroche and Grigaut¹ and by Schmidt.² Considering the various types of Bright's disease in their broad aspects, it is true that in those forms in which the blood urea nitrogen is normal or but slightly elevated are those in which the plasma cholesterol is high, *e. g.*, chronic diffuse glomerular nephritis with a "nephrotic" component. The converse, a low plasma cholesterol and marked nitrogen retention, is not as clear as this. Throughout the tables presented, it will be observed that fluctuations in the urea nitrogen content of the blood are often accompanied by inverse changes in the plasma cholesterol; at other times, the tendency to such an adjustment is offset by various compensatory factors which render it difficult to note such a relation uniformly. Recent investigations carried out in this laboratory have shown that an increment in the blood urea following the ingestion of urea by human subjects is often accompanied by a striking diminution of the plasma cholesterol;¹⁵ this reciprocal relation, however, is observed more frequently experimentally than clinically.

(b) We were unable to observe any constant relation between the plasma cholesterol and the total plasma proteins. Van Slyke and his associates¹⁶ found that the plasma proteins tend to rise before death from renal insufficiency; in many of our fatal cases a terminal rise was observed. It might be assumed that the cholesterol falls as the proteins rise in order to maintain osmotic balance (Fishberg¹⁷). Yet, in Table 3 total plasma proteins of 6.2 gm. per cent and 6.9 gm. per cent are accompanied by a high cholesterol, while an extremely low plasma protein (2.5 gm. per cent in Case 22) is associated with a decreased cholesterol (161 mg. per cent). A subnormal plasma cholesterol (83 mg. per cent; 112 mg. per cent) in Case 3, Table 1, is not accompanied by a high plasma protein content (as might be expected if the osmotic pressure adjustment theory held true) but in fact by a low value (4.7 gm. per cent). Thus, the possibility is suggested that other compensatory factors tend to modify and, at times, even nullify this inverse relation between the cholesterol and protein content of the plasma, which theoretical and experimental considerations would lead us to believe probably exists.

II. The hypocholesterolemia observed in uremia may represent the usual finding in cachexia.¹⁸

III. The low plasma cholesterol observed in patients with non-nephritic anemia (pernicious anemia, chlorosis, aplastic anemia, etc.) has been recorded by many observers. Muller¹⁹ and Peters and Van Slyke¹⁵ have recently reviewed the literature on this subject. Table 4 shows a representative group of 10 non-nephritic patients with marked cachexia and anemia. The extremely low

plasma cholesterol observed in such instances is evident from the protocol. It appears probable, therefore, that the diminished cholesterol content of the plasma observed in cases of Bright's disease dying of retention uremia may be due to such contributing factors as cachexia and anemia.

Conclusions. 1. In cases of chronic Bright's disease with marked nitrogen retention, a low plasma cholesterol foretells death in uremia. In most cases this low reading is observed at an appreciable interval before death; in rare cases such a level is found only about 24 to 48 hours before exitus.

2. An elevated plasma cholesterol indicates a good prognosis as to recovery from pre-uremic symptoms but does not preclude the possibility of death from causes other than uremia.

3. There appears to be no close relation between the height of the plasma cholesterol and the degree of edema in patients with chronic Bright's disease.

4. There is some clinical evidence of a reciprocal relation between the blood urea and the plasma cholesterol; at other times this relation is offset by other factors. A constant inverse relation between the plasma proteins and cholesterol was not observed.

5. The diminished cholesterol content of the plasma observed in cases of Bright's disease dying of retention uremia is probably due to such contributing factors as cachexia and anemia.

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ACCIDENTAL HYPODERMIC TRANSMISSION OF MALARIA IN DRUG ADDICTS.

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Two malarial patients, habitually taking heroin intravenously, entered Cook County Hospital in December, 1932. Neither patient had recently inhabited a recognized malarial district. Both denied previous attacks of chills and fever. One of the patients stated that many of his addict friends were similarly ill with chills and fever. However, they avoided hospital treatment for fear of reduction or withdrawal of their drugs. A laboratory technician, who had worked in this particular ward for 4 years, observed that he had never seen a malarial patient who was not a drug addict.

We suspected that the disease was accidentally transmitted when we learned of the non-sterile technique and the habit of group injection practised by the drug addicts. It is their custom to congregate in groups of 3 to 12 or more for administering the drugs. Heroin is most frequently used at present, due to the prohibitive cost of morphin. The drug is dissolved in tap water. The solution is drawn into a medicine dropper. Strips of paper are wrapped around the tip of the dropper so that the hypodermic needle can be attached. The first recipient inserts the needle into a vein, at which time blood flows back into the barrel of the dropper. Then, he injects his portion of the drug. The hypodermic outfit and remaining contents are then passed to others of the group, who repeat the process. The instruments are never sterilized.

Artificial transmission of malaria is common in the treatment of general paresis. Accidental transmission has occurred in blood transfusions as described by Korabelnikoff¹ and Decourt.² Wenyon³ described the infection of 10 men with malignant tertian malaria by non-sterile administration of salvarsan. The apparatus consisted of a receptacle, rubber tube with glass tube window, and sterile needle. The needle was inserted, the receptacle lowered so that blood flowing back to the window indicated that the needle was in place. The needle, but not the tube, was changed for each injection. Netter⁴ reported a similar case.

Knowing the above facts, we can assume that the methods in vogue among the addicts of Chicago would tend to the dissemina-

tion of malaria from those afflicted with the disease. We undertook this study, seeking evidence for the transmission of malaria among addicts by the hypodermic needle and the importance of this mode of spread.

Methods of Study. First, we attempted to examine as many addicts as possible for malaria. In spite of coöperation given us by 2 addict malarial patients whom we had treated, their friends refused to come for examination. Some feared legal retention and others withdrawal of heroin.

Second, thwarted in the first plan, we turned to the analysis of the case histories of all patients diagnosed as malarial in Cook County Hospital from January 1, 1925, to March 5, 1933.

We utilized the histories of 197 patients. Of these, the parasite was demonstrated in 163 instances. In the charts of the remaining 34 patients, none addicts, the typical history and course, the finding of a palpable spleen, and the immediate response to quinin therapy forbade their discard as non-malarial.

For purposes of study we found it convenient to divide the cases into the following three groups:

1. Those found to be addicts.
2. Those non-addicts who gave a history of recurrent attacks of malaria or primary infection most probably contracted in the South.
3. Those non-addicts who denied exposure outside of Chicago and its environs.

Analysis of Histories. In 170 histories a definite statement as to locality of possible contraction of malaria occurred. Of these, 112 patients, exclusive of addicts, undoubtedly contracted the disease in the Southern states. Thirty-eight patients, who were not found to be drug addicts, denied exposure outside of the Chicago area. Twenty were morphin or heroin addicts and only 1 of these could have contracted the disease in the South. Thus, we found, with one exception, that addicts with malaria did not give the usual history of onset or recent exposure in a recognized malarial district.

Figure 1 presents data as to the time of onset of malaria in the three groups comprising 170 patients. The onset in the addicts with malaria was quite evenly distributed throughout all months of the year. The onset in non-addicts, contracting the disease in Chicago, occurred only between July and October, inclusive. In those contracting the disease in the South or suffering recurrent attacks, the onset was most frequent in the summer and early fall months. Thus, we found the onset of malaria in drug addicts to show no seasonal increase, as in natural infection, but to occur as one would predict if the infection were accidental and artificial.

Figure 2 presents data as to the number of each group of malarial patients admitted to Cook County Hospital during each year studied. From 1925 to 1930, only the occasional malarial patient was found to be a drug addict. In 1931 and 1932, the number of

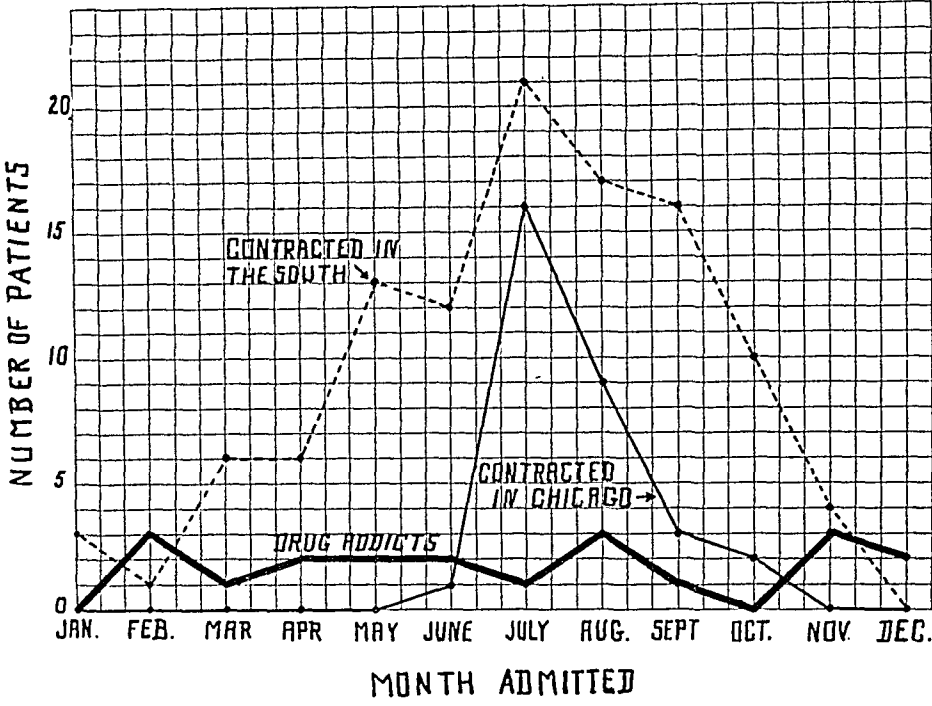


FIG. 1.—Month of onset of malaria in addicts and non-addicts.

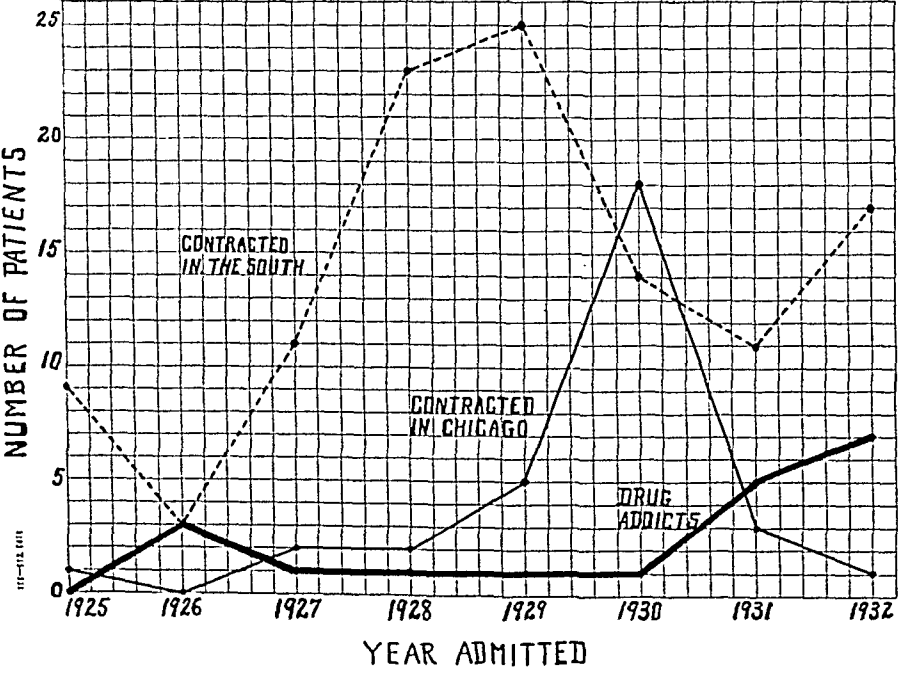


FIG. 2.—The total number of patients (nearest round numbers) admitted to Cook County Hospital during the years studied were as follows: 1925, 41,000; 1926, 41,000; 1927, 43,000; 1928, 48,000; 1929, 48,000; 1930, 50,000; 1931, 56,000; 1932, 63,000.

addict malarial patients definitely increased, out of proportion to the increase in total admissions. In the latter year 35 per cent of all adult male malarial patients admitted to this hospital were heroin addicts taking the drug hypodermically. The number of patients contracting the disease in the South definitely decreased after 1929, although total admissions increased. The number of non-addict patients contracting malaria in Chicago remained about the same except for a marked increase in 1930. In that year more patients contracted the disease in Chicago than in the South.

During the period studied, there were 20 histories of malaria in drug addicts. This included 17 patients, 3 being readmitted once. All habitually took morphin, heroin, or both, either intravenously or subcutaneously. The malarial parasite was demonstrated in every case. In 14 of the 17 patients it was identified as *Plasmodium vivax*. Seven patients suffered single infection and 7 others a double infection. In the charts of 3 patients, the specific identity of the parasite was not recorded. All patients were adult white males. Patient "A" knew 7 of the other 16 patients and admitted sharing injections with 4 of them. Patient "B" knew 5 and remembered injections with 2 of them.

In reviewing the literature, we found that Biggam,⁵ in August, 1929, reported 10 cases of malignant tertian malaria in patients who habitually took heroin intravenously. All were inhabitants of Cairo, Egypt, where this type of malaria was "almost unknown" among non-addicts. Therefore, he concluded that the infection was conveyed by the use of unclean hypodermic outfits. Dr. Arafa,⁶ writing in April, 1930, stated that Biggam and his colleagues had now observed over 100 such cases.

Summary. We present this paper to corroborate Biggam's original observation of the accidental hypodermic transmission of malaria among heroin addicts. The following observations support his conclusions:

1. The relatively high incidence of drug addiction among the malarial patients of our series.
2. The absence of the usual history of onset or recent exposure in the South given by malarial patients who were drug addicts.
3. The onset in addicts was distributed evenly throughout the months of the year, as one would predict of accidental artificial transmission.

We wish to call to the attention of American physicians this etiologic factor, which in recent years has become an important one at Cook County Hospital.

During the first 5 months of 1933, there have been 9 additional instances of malaria in the wards of Cook County Hospital. Of this number 1 was a woman and 8 were men. Six of these 9 cases were morphin or heroin addicts and only 1 of this group had been South. Of the 3 patients who were non-addicts 1 was a woman who apparently contracted malaria in Chicago and 2 were men who gave a definite history of the symptoms beginning in the South.

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THE CORRECTED SEDIMENTATION RATE (C.S.R.) IN SCARLET FEVER.

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SINCE 1918, when Fahraeus rediscovered the phenomenon of blood sedimentation, most of the vast literature concerning this subject has been devoted to its study in tuberculosis, rheumatic and gynecologic conditions. Relatively little has been published about the blood sedimentation test in acute infectious diseases, such as scarlet fever. The conflicting reports from Germany and the lack of a single American contribution to this subject prompted the author to investigate the blood sedimentation rate in scarlet fever.

Büchler,^{1,2} in 1925, was the first to report on the blood sedimentation rate in this disease. In a series of 35 cases he found the fall of the sedimentation rate, repeated at regular intervals, so characteristic that he felt a differential diagnosis could be made by means of it. He called this typical curve the "Normal-Senkungs-Kurve" (N-S-K) and described it as gradually declining from an initially elevated level until it reached a normal figure on or about the 25th day of the disease. In cases which developed complications, there were aberrances from the typical curve and the return of the rate to normal would be delayed beyond the usual time. Unfortunately, nobody save Rohrbösch,³ with a series of only 8 cases, has been able to corroborate Büchler's results.

Rhodin's^{4,5,6} findings in 70 cases differed greatly from those of Büchler. He felt that the curves all showed the following common characteristic: from a more or less elevated level, the curve suddenly descended to a considerably lower value, from which it ascended again to its previous position. This oscillation, called the "characteristic phase," recurred at intervals of 3 to 6 days, and through the presence of these phases the sedimentation curve ran in repeated and more or less regular waves. Rhodin further differentiated two types of curves: in the first, the rate gradually fell, reaching a normal level by the 4th to the 6th week or occasionally earlier;

in the second, the rate declined until about the 3d week and then showed a marked rise again. In both types of curves, however, the presence of the "characteristic phase" was manifest, and it was in this respect that the curve in scarlet fever differed from that found in other diseases.

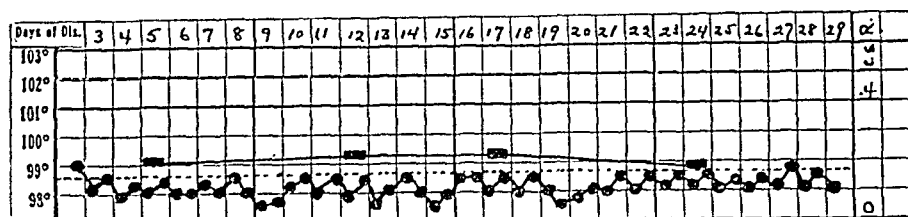
Other investigators have failed to corroborate either Rhodin or Büchler; Stoltenberg⁷ could find no typical curve in 172 cases. Pulver⁸ likewise failed to find a typical curve. He had cases in which there were no complications, where the rate was still elevated in the 6th week after the onset of illness. Wylie,⁹ Rees Walton,¹⁰ and Grenet, *et al.*,¹¹ make brief mention of the test in scarlet fever but present no cases in which the test was repeated at regular intervals.

Methods. In the present study, the technique of Rourke and Ernstone¹² was followed (rate of 0.35 mm. per minute as the normal limit). In a previous study,¹³ the author raised this maximal normal value so as to include all readings up to 0.40 mm./min. Readings from 0.40 to 0.60 were termed moderately elevated; 0.60 to 0.90, elevated; and 0.90 and over, greatly elevated. The same standards are used in this study, save that readings 1 mm./min. and over are called greatly elevated.

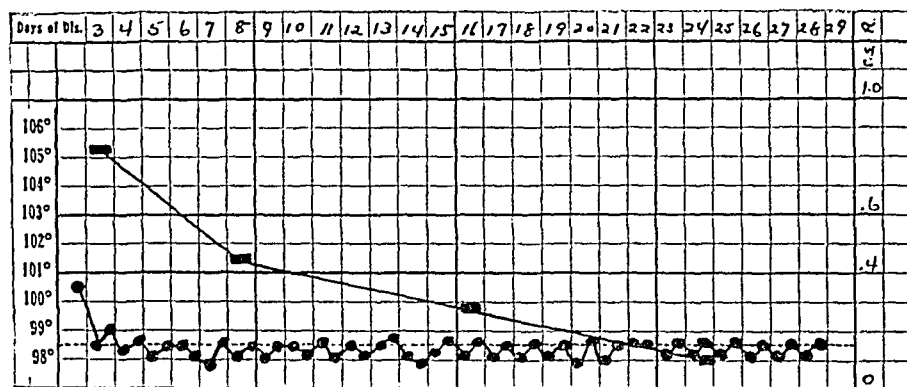
Fifty-five cases of scarlet fever at the South Department of the Boston City Hospital were followed by means of the blood sedimentation rate, or more properly, the corrected sedimentation rate (C.S.R.). The patients ranged in age from 4 to 55 years. Each case had at least 1 weekly determination. The first few cases had 2 determinations during the first week of illness in an effort to see if there was any change in the C.S.R. with the disappearance of the rash. Inasmuch as no effect was noticed, this was not continued.

Results. Proper emphasis on the fact that the fall of the sedimentation rate depends a good deal on the severity of the case, does not seem to have been made by previous observers. Charts I to IV illustrate the typical course of the sedimentation rate in cases of scarlet fever ranging in severity from very mild to severe. In very mild cases, which show no fever or constitutional symptoms, there may be no elevation of the rate at any time. These cases are, however, uncommon. In ordinary mild cases, the curve shows the C.S.R. elevated at first, but falling fairly promptly and reaching a normal level during the second week of the disease. Save for the mild cases, the C.S.R. did not reach a normal level after the routine 4 weeks of hospital stay, even in uncomplicated cases. This agrees with Pulver's findings, where many cases showed elevated rates, even during the 5th and 6th week after onset. In only 12 of my 55 cases was the C.S.R. normal on discharge from the hospital. In Case 87919 (Chart III), a fairly typical moderate case of scarlet fever, the C.S.R. was somewhat lower on the 32d day than it was

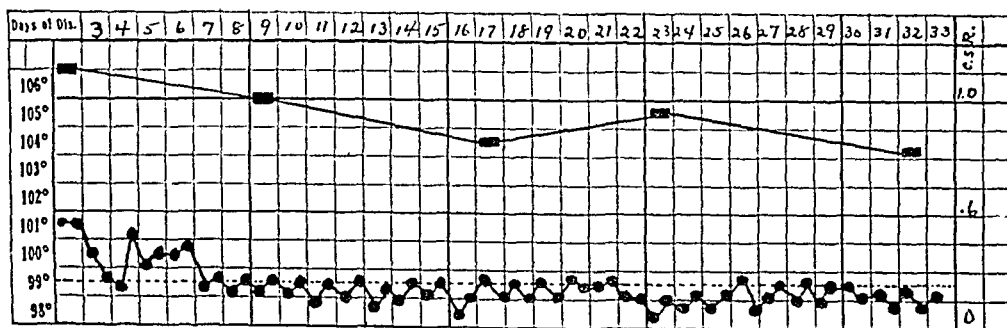
on entry, but was still elevated. The rate in severe cases, as typified in Chart IV, remained at a greatly elevated level throughout the entire hospital stay. It may be seen, then, that there is no



Temp. curve. CHART I.—Case 87965, M., age 10. Very mild, uncomplicated case of scarlet fever.
C.S.R.

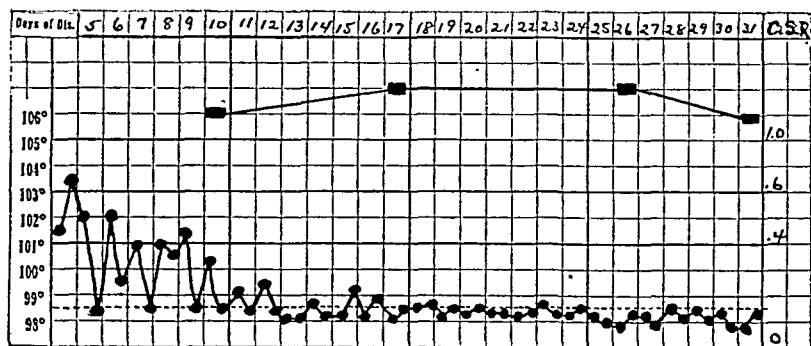


Temp. curve. CHART II.—Case 87853, F., aged 8. Mild, uncomplicated case of scarlet fever.
C.S.R.



Temp. curve. CHART III.—Case 87919, M., aged, 9. Moderate, uncomplicated case of scarlet fever.
C.S.R.

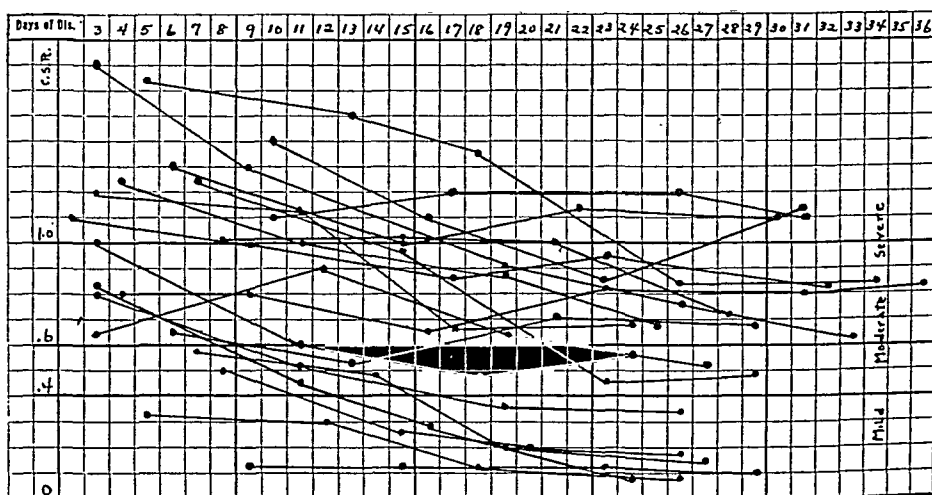
typical curve for the decline of the sedimentation rate in scarlet fever, the curve depending greatly on the mildness or severity of the case. Chart V shows the variability of the curve in a series of uncomplicated cases ranging from very mild to severe. Obviously,



Temp. curve.

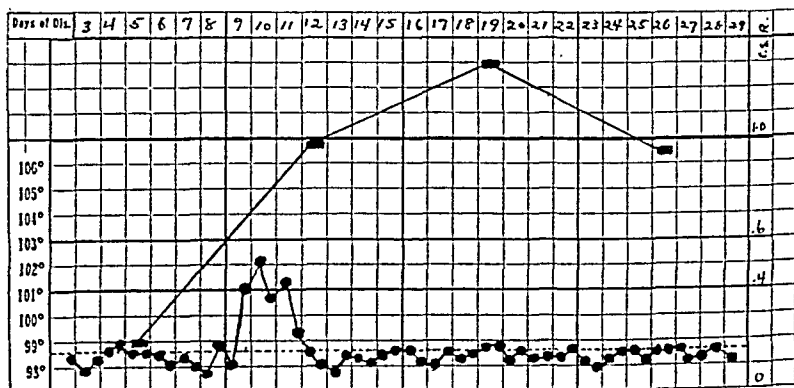
CHART IV.—Case 88017, F., aged 26. Severe, uncomplicated case of scarlet fever.

C.S.R.



C.S.R.

CHART V.—Uncomplicated cases of scarlet fever, showing variation in sedimentation curves.

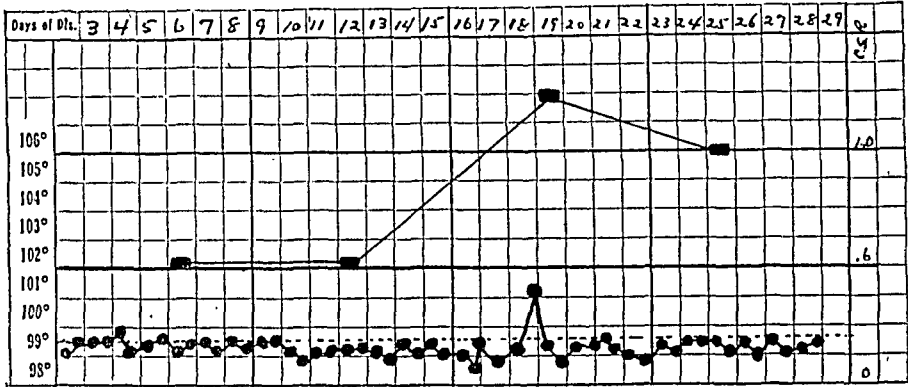


Temp. curve.

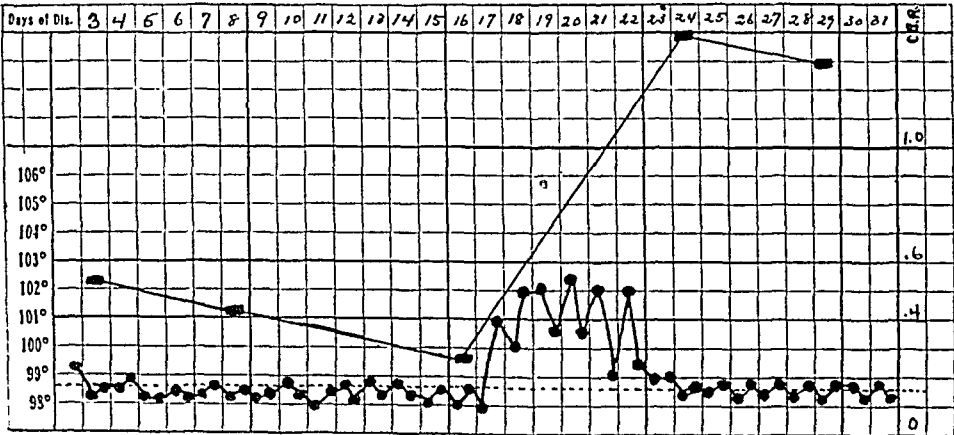
CHART VI.—Case 88006, M., aged 22. Very mild case of scarlet fever, complicated on the 9th day by a streptococcus sore throat.

C.S.R.

then, as there is no typical curve, we cannot use it as a differential point. In fact, an ordinary streptococcus sore throat will give a sedimentation curve like that of a case of scarlet fever, as may be seen in Chart VI. At the onset of this very mild case, there was no fever and the C.S.R. was normal. The clinical course was complicated on the 9th day by a fairly severe streptococcus sore throat which produced a persistently elevated C.S.R., whose course certainly cannot be differentiated from the curve in a fairly severe case of scarlet fever.



Temp. curve. CHART VII.—Case 87995, F., aged 7. Mild case of scarlet fever, complicated on the 18th day by cervical adenitis.
C.S.R.



Temp. curve. CHART VIII.—Case 87860, F., aged 10. Mild case of scarlet fever complicated on the 17th day by a severe general arthritis.
C.S.R.

Complications. The presence of a complication may be reflected in one of several ways in the sedimentation curve. If the C.S.R. is not too high or is falling, a complication, even though slight, will manifest itself by a distinct rise in the C.S.R., as may be seen in Chart VII. The onset of a cervical adenitis in the course of this mild case of scarlet fever caused a distinct rise in the C.S.R. If,

however, the rate is already high, the appearance of a complication may not produce any further change. Complications, of course, will keep the rate elevated much longer than it ordinarily would be. Büchler felt that the sedimentation rate began to rise several days before the onset of a complication and thus might serve as a warning signal. Stoltenberg could not confirm this. The author too, has not found that the sedimentation rate, as a rule, serves as a warning beacon before the complication actually sets in. As an example, in Case 87860 (Chart VIII) the C.S.R. was normal the day before the onset of a severe arthritis.

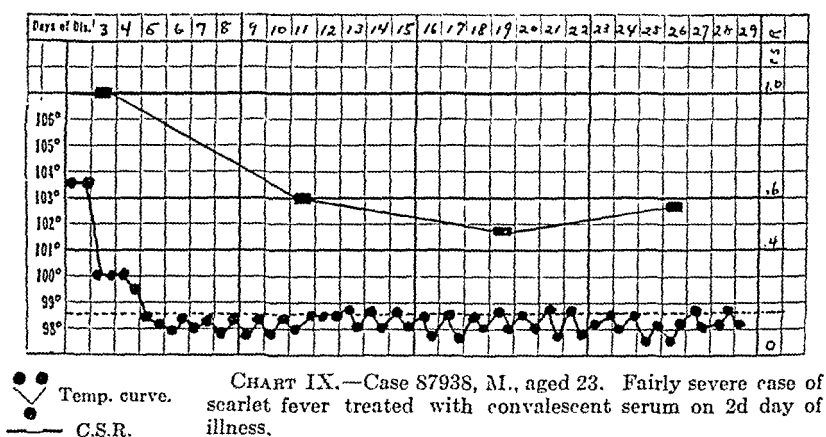


CHART IX.—Case 87938, M., aged 23. Fairly severe case of scarlet fever treated with convalescent serum on 2d day of illness.

Effect of Serum and Antitoxin.—There have not been any previous observations made on the effect of the administration of convalescent serum or antitoxin on the sedimentation curve in scarlet fever. It is rather difficult in this series in which, following the regular hospital routine, serum was given to severe cases only, to draw any definite conclusions as to the effect of convalescent serum on the course of the C.S.R. Chart IX illustrates the most gratifying result obtained. This was a fairly severe case in which convalescent serum was given on the second day of illness. There is a distinct fall and maintenance at only a moderately elevated level in the C.S.R., which was not seen in any untreated case of equal severity. All the other serum treated patients, however, left the hospital with elevated or greatly elevated rates, and the course of the C.S.R. did not show any distinct fall. It was not possible to draw any conclusions at all as to the effect of antitoxin on the course of the C.S.R., as the few cases that received antitoxin all developed serum reactions which kept the rate elevated.

Comment. The most important practical question is naturally whether the determination of the sedimentation rate in scarlet fever is of any value to the clinician. I would say definitely that in comparison with chronic conditions such as tuberculosis or rheumatic fever where the sedimentation rate is highly important

as the best and frequently the only measure of activity, the determination of the rate in acute conditions, such as scarlet fever, is not of great importance or value. As a rule, the clinical picture in an acute illness, such as scarlet fever, is a sufficient guide. Possibly, in certain instances, for example, cases complicated by a general arthritis where the picture may greatly resemble rheumatic fever, regularly repeated determinations of the C.S.R. may be of value in evaluating the subsidence of activity. As for using the sedimentation curve as an aid in differential diagnosis, we have seen that the curve is far too variable to be of any assistance.

Summary. 1. Fifty-five cases of scarlet fever were followed by means of the corrected sedimentation rate (C.S.R.).

2. The curve of the sedimentation rate varied with the mildness or severity of the case. In the majority of cases, the C.S.R. had not returned to normal when the patients left the hospital.

3. Complications were manifested by a rise in the C.S.R. If the rate were already distinctly elevated, a complication might produce no further rise.

4. It was not possible to draw any definite conclusions as to the effect of the administration of convalescent serum or antitoxin on the sedimentation curve.

NOTE.—The author welcomes this opportunity to express his gratitude to Dr. Edwin H. Place, physician-in-chief, for permission to use the cases on his wards.

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THE INDUCTION OF EOSINOPHILIA IN NORMAL ANIMALS.

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MARKED eosinophilia has been observed as a symptom of many diseases, such as asthma, ankylostomiasis, filariasis, trichinosis and serum sickness. During the course of numerous acute infections,

the relative number of eosinophils fluctuates; the appearance of eosinophilia, according to Schilling,¹ indicates a favorable prognosis. The induction of eosinophilia in normal animals, therefore, may lead to an understanding of its relation to pathologic states.

Many workers have induced eosinophilia experimentally. The literature of the earlier attempts with worm extracts was ably reviewed by Wells² in 1920. In 1925, we reported³ a high eosinophil count occurring in a rabbit in which the trachea was obstructed and attributed it to a disturbance in the acid-base equilibrium of the body fluids, a view that the recent literature would seem to support.

Pescatori,⁴ who considered all types of eosinophilia to be characterized by asphyxia, induced the condition locally in the extremities by constriction; $\frac{1}{2}$ hour after normal circulation was restored, he found an eosinophilia of from 4 to 9 per cent. When a general asphyxia was induced by injecting fluid into the trachea, the eosinophils rose from 12 to 30 per cent.

Vacca⁵ fed copper sulphate to guinea pigs over considerable periods of time and found a marked increase in the eosinophils. He attributed this action to the copper ion, disregarding any possible effect which the acid radical might have had on the acid-base equilibrium.

Hajós, Németh, and Enyedy⁶ increased the eosinophil count in 8 out of 10 rabbits by stimulation of the vagus nerve with Faradic current for from $\frac{1}{2}$ to 8 hours. In their protocols, the authors record the fact that all of their animals were "very dyspneic" or "nearly dead" after 1 hour of stimulation. Aside from the authors' conclusions concerning this experiment, it is very evident from their data that profound changes must have occurred in the rate of elimination of carbon dioxide to produce dyspnea and death.

Numerous reports have appeared in recent years on the use of the barbituric-acid derivative called "nirvanal" in the treatment of chorea. Daily administration of this drug produces in man a syndrome called "nirvanal sickness," characterized by fever, an exanthematous rash, and a pronounced eosinophilia. De Rudder⁷ has studied this peculiar condition and reports that the reaction of the urine is alkaline during the incubation period of the disease but becomes acid with the eruption of the rash, coincident with the appearance of a high degree of eosinophilia in the blood stream.

Among recent reports upon the experimental production of eosinophilia, there are 5 which have no particular bearing on the study that forms the subject of this paper, except for one common factor: each method has interfered with the elimination of carbon dioxide, or has altered the acid-base balance toward the acid side in some other manner.

It appears, then, that a disturbance in the acid-base equilibrium, either local or general, may produce a variety of changes in the blood and other organs. When an infection, toxin or drug, has an

opportunity to influence this system, it may upset the equilibrium. Deviations in the acid-base balance may be responsible for stimulation, growth, inhibition, or death of cells or cell groups.

Experimental Work. In this study of the effects of exposure to increased amounts of carbon dioxide, rabbits were used as experimental animals because of the facility with which they can be given intravenous solutions. It should be noted that the rabbit's polymorphonuclear leukocytes contain acidophilic granules and indeed some authors⁸ refer to them as pseudo-eosinophils. All blood film preparations were allowed to dry in air, were then fixed and stained with Wright's stain, and were examined with an oil-immersion lens by artificial light.

The solution of carbon dioxide was prepared by bubbling the gas from a Kipp generator through 0.85 per cent sodium-chloride solution, which was chilled by immersion in a pail of ice. The carbon-dioxide solution was kept in the refrigerator when not in use, and at other times on ice. It was standardized by titration with $\frac{N}{10}$ sodium hydroxide. After the syringes had been sterilized and chilled, the carbon-dioxide solution was drawn into them and they remained on ice until the injections were given.

In the second part of the work, the experimental animals were placed in a large museum jar, the wooden cover of which was held in place against a rubber gasket by a clamp. One ear of the rabbit was drawn through a hole in the cover in order that specimens of blood might be taken at frequent intervals. Moistened carbon dioxide was admitted through a second hole; through the third, there projected an outlet tube with a two-way stopcock which on one side communicated with the outside air and served to maintain atmospheric pressure in the jar and on the other was connected, by means of rubber tubing, with a gas burette. Samples of the air in the jar were withdrawn several times during each experiment and the percentage of carbon dioxide it contained was determined by absorption in normal sodium-hydroxide solution.

Results. The averages of the differential blood counts of 5 normal rabbits before the administration of carbon dioxide were as follows: 30.59 per cent polymorphonuclear leukocytes, 60.7 per cent lymphocytes, 3.3 per cent large mononuclears, 0.43 per cent eosinophils, 4.8 per cent basophils.

Table 1 gives the result of the first intravenous administration of carbon-dioxide solution. The eosinophil percentage increased from 0 to 2.5 in 30 minutes; 23 hours later, it was still high. Repetition of the experiment on the same animal on 2 successive days was without significant effect. In a fresh rabbit, the eosinophils were slightly increased after the administration of carbon-dioxide solution but they rapidly fell to normal (Table 2). Table 3 records a control experiment in which ice-cold salt solution containing no carbon dioxide was used.

In the second portion of the work, more encouraging results were obtained. In Table 4, figures for the first rabbit confined in the jar are given. No samples of air in the jar were collected during the first part of the experiment but the increase in the eosinophils was twenty-fold. The rabbit was removed from the jar when he lost consciousness and was replaced $1\frac{1}{2}$ hours later. Within 5 minutes, his eosinophil count rose to 8 per cent, 32 times what it had

been less than 2 hours before. The final concentration of carbon dioxid in the jar was 26.89 per cent. The relative number of eosinophils still remained high 24 hours later.

TABLE 1.—THE EFFECT UPON THE DIFFERENTIAL LEUKOCYTE COUNT OF THE INTRAVENOUS INJECTION OF 2 CC. OF PHYSIOLOGIC SALT SOLUTION CONTAINING 1060 MG. OF CO₂ PER LITER. (RABBIT No. 3746.)

Time of cell count.	Poly-morpho-nuclears, per cent.	Lympho-cytes, per cent.	Large mono-nuclears, per cent.	Eosino-phils, per cent.	Baso-phils, per cent.	No. of cells counted.
11.14 A.M.	33.0	57.0	3.00	0.00	7.0	436
During injection*	46.0	47.0	1.00	0.00	6.0	344
During injection*	56.0	51.0	1.00	1.00	1.0	267
11.29 A.M.	55.5	38.0	0.75	0.75	5.0	289
11.44 A.M.	49.0	43.0	0.50	2.50	5.0	451
10.00 A.M. (23 hours later)	43.0	49.0	5.00	0.90	2.1	328

* Two samples of blood were taken during the injection period, which required 1.5 minutes.

TABLE 2.—THE EFFECT UPON THE DIFFERENTIAL LEUKOCYTE COUNT OF THE INTRAVENOUS INJECTION OF 5 CC. OF PHYSIOLOGIC SALT SOLUTION CONTAINING 1000 MG. OF CO₂ PER LITER. (RABBIT No. 3777.)

Time of cell count.	Poly-morpho-nuclears, per cent.	Lympho-cytes, per cent.	Large mono-nuclears, per cent.	Eosino-phils, per cent.	Baso-phils, per cent.	No. of cells counted.
11.30 A.M.	33.0	56.0	4.5	0.6	5.9	318
During injection*	33.0	57.0	4.0	0.4	5.6	484
During injection*	38.0	52.0	4.2	1.0	4.8	282
During injection*	40.0	49.0	4.2	0.9	5.9	437
11.45 A.M.	50.0	36.0	4.6	0.4	9.0	433
12.00 NOON	43.0	47.0	3.2	0.3	6.5	217
1.20 P.M.	42.5	42.0	4.5	0.0	6.5	

* Three samples of blood were taken during the injection period, which required 1.5 minutes.

TABLE 3.—THE EFFECT UPON THE DIFFERENTIAL LEUKOCYTE COUNT OF THE INTRAVENOUS INJECTION OF 2 CC. OF PHYSIOLOGIC SALT SOLUTION CONTAINING NO CO₂.* (RABBIT No. 3776.)

Time of cell count.	Poly-morpho-nuclears, per cent.	Lympho-cytes, per cent.	Large mono-nuclears, per cent.	Eosino-phils, per cent.	Baso-phils, per cent.	No. of cells counted.
Control count	40.0	53.0	5.0	0.0	2.0	200
Injection begun	42.0	53.0	2.0	0.4	2.6	200
Injection finished	34.0	55.0	8.0	0.0	3.0	200
15 minutes later	40.0	52.0	6.0	0.0	2.0	200
30 minutes later	40.0	50.0	3.1	0.6	6.1	200

* 1.5 minutes were required for the injection.

TABLE 4.—THE EFFECT OF INCREASING THE CO₂ CONCENTRATION OF AIR UPON THE EOSINOPHIL COUNT. (RABBIT No. 3778.)

Time of cell count.	CO ₂ * per cent.	Poly- morpho- nuclears, per cent.	Lympho- cytes, per cent.	Large mono- nuclears, per cent.	Eosino- phils, per cent.	Baso- phils, per cent.	No. of cells counted.
Control count	27.0	65.75	4.5	0.25	2.5	341
2:02 P.M.	47.0	42.90	3.1	2.50	4.9	300
2:07 P.M.	51.0	33.20	3.8	5.10	6.9	250
<i>Intermission.</i> †							
3:50 P.M.	11.68	41.0	49.00	3.0	3.00	4.0	235
3:55 P.M.	26.89	47.0	33.00	6.0	8.00	6.0	200
24 hours later	40.0	46.70	3.9	5.50	3.9	250

* Blanks indicate that the percentage of CO₂ was not determined.

† Rabbit lost consciousness and was removed from jar for 1.5 hours.

In a similar experiment with another rabbit, there was an initial rise in the eosinophils from 0.4 per cent to 1.7 per cent, followed by a drop to 1.4 per cent as soon as the animal was removed from the jar. There was a secondary rise to 3.4 per cent, which became apparent when a count was taken the next day.

Summary and Conclusions. 1. An elevation in the relative number of eosinophils was induced in rabbits subjected to increased carbon-dioxid tension in the blood, either by intravenous administration of carbon-dioxid solutions or by exposure of the animal to an atmosphere containing increasing amounts of this gas.

2. From this result, it is concluded that an alteration in the acid-base equilibrium of the body appears to incite an eosinophilia.

Further studies, it is hoped, will lead to a better understanding of the mechanism of this alteration.

I desire to express appreciation of the advice which I have received from Dr. C. C. Torrance throughout the work and in the presentation of the results.

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CHRONIC IDIOPATHIC HYPOCHROMIC ANEMIA.

ETIOLOGIC RELATIONSHIP OF ACHLORHYDRIA TO THE ANEMIA, WITH SPECIAL REFERENCE TO THE EFFECT OF LARGE DOSES OF IRON, ORGANIC (DIETARY) IRON AND OF PREDIGESTED FOOD UPON FORMATION OF ERYTHROCYTES.*

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DURING recent years the relationship between certain dietary factors and formation of erythrocytes has been demonstrated by Whipple¹ in the experimental anemia of dogs; and that of liver to pernicious anemia by Minot and his associates.² In addition, it has been clearly shown by Castle,³ in his studies on the relationship of achylia gastrica to pernicious anemia, that it is necessary not only to ingest adequate amounts of food to insure proper nutrition, but also that it is equally essential that proper digestion and absorption of nutritional elements take place to prevent the development of certain deficiency states. One of the conditions in which there is a failure of the marrow to produce normal erythrocytes, and in which defective diet and improper function of the gastro-intestinal tract may be implicated, is chronic idiopathic hypochromic anemia.

Among patients with chronic hypochromic anemia will be found a group consisting especially of middle-aged women who subsist on a diet low in iron-containing food, and in whom gastric achlorhydria or hypochlorhydria is a constant feature. This condition apparently constitutes a distinct clinical entity. During the past few years, increasing numbers of reports of this condition have appeared in the medical literature, and have been classified variously as chronic chlorosis,⁴ microcytic anemia,⁵ simple achlorhydric anemia,⁶ idiopathic hypochromic anemia⁷ and by other

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terms.^{8, 9, 10} Although the mechanism which produces anemia in these patients is unknown, it seems plausible that it may be primarily dependent upon an abnormality in the metabolism of iron. It appears in some cases that the symptoms are intensified by chronic loss of blood, pregnancy,¹¹ or some other factor,¹⁵ or following partial extirpation of the stomach. Since defective diet and achlorhydria or hypochlorhydria are constantly present,^{12, 13, 14, 15, 16, 17} the questions arising for solution are: (1) is the anemia due to an inadequate intake of iron-containing foods? or, (2) is an abnormality of gastric digestion responsible for the anemia? It is the purpose of this paper to report the results of some experiments made in an endeavor to evaluate these factors by controlled observations on a series of 10 cases.

Method of Study and Nature of Cases. A gastric analysis was performed on the 10 patients. The amount of free hydrochloric acid as well as the total acidity were determined. The presence or absence of pepsin in the gastric secretion was estimated by the egg-albumen digestion method. An attempt to stimulate gastric juice secretion, following the removal of specimens of fasting content, was done by the oral administration of 50 cc. of 7 per cent alcohol, and, again, after the subcutaneous injection of 0.25 mg. of histamin.

All of the 10 patients studied were females. They ranged in age from 23 to 46 years. Some of the women had been pregnant, and one (Patient 10), with chlorotic anemia of pregnancy,¹² was 4 months pregnant at the beginning of our studies on her. One (Patient 8*) developed a hypochromic anemia after a partial gastric resection. She had been operated upon in 1914 and a gastroenterostomy performed, with the hope of giving relief from symptoms of peptic ulcer. In 1928 another operation was performed because the gastroenterostomy failed to function properly and, after removal of approximately two-thirds of the stomach, the remaining cardiac portion was anastomosed with the jejunum, thus leaving a blind pouch of the duodenum. Since then, the patient had been free of symptoms of ulcer but had developed a progressive anemia. In none of the patients was there a history of chronic loss of blood or recent infection, and in none could a malignancy be demonstrated as responsible for the anemia.

The anemia of all was distinctly chronic and of the so-called hypochromic type with a color index of less than one. Some of the patients were known to have been anemic for years and had been given various therapeutic preparations by mouth and injections of iron at varying intervals since childhood.

A history of all of the patients' dietary habits was elicited in a painstaking manner. Careful questioning revealed that the diet of all of these women was deficient in the amount of meats, fruits

* We wish to thank Dr. J. Homer Woolsey for permission to study this case.

and green vegetables consumed. The total calories, composed mostly of carbohydrate foods, were apparently adequate, for, with the exception of 3 women who were undernourished, they were all of normal weight or were overweight. Most of the patients seldom ate meat or eggs; others partook of these products perhaps on an average of 3 times a week in small portions. In most instances the patients stated that their dietary habits had been irregular since childhood and that their appetites were usually appeased with starchy foods and small portions of fruits or vegetables. One of the outstanding characteristics of the diets was the lack of iron-containing foods.

Throughout certain phases of the observations, total red cell counts and hemoglobin determinations were made at weekly intervals, and, during other phases of the experiments, daily examination of the blood was done including reticulocyte counts. The hemoglobin concentration was determined with a Sahli hemometer, with tubes calibrated so that 100 per cent equalled 17 gm. of hemoglobin per 100 cc. of blood.

TABLE 1.—CLINICAL DATA.

Patient No.	Sex.	Age.	Nature of case.	Gastric secretion.
1 . . . (I. G.)	F	42	Defective diet for years; twice pregnant; overweight	No free HCl after histamin; peptic activity normal.
2 . . . (M. H.)	F	27	Defective diet; undernourished; recent pregnancy	No free HCl after histamin; peptic activity normal.
3 . . . (L.)	F	36	Defective diet; normal weight; twice pregnant	No free HCl after histamin; peptic activity normal.
4 . . . (D. C.)	F	36	Deficient diet; undernourished; "anemic" since childhood; three times pregnant	No free HCl; 15 cc. N/10 acid per 100 cc. gastric juice after histamin; peptic activity normal.
5 . . . (M. W.)	F	46	Defective diet; known to have been "anemic" 5 years; normal weight	No free HCl after histamin; peptic activity normal.
6 . . . (K. V.)	F	23	Defective diet; undernourished	No free HCl after histamin; peptic activity normal.
7 . . . (G. S.)	F	36	Defective diet; slightly overweight; "anemic" 4 years; twice pregnant	No free HCl after histamin; peptic activity normal.
8 . . . (A. H.)	F	46	Gastroenterostomy 1914 for peptic ulcer relief; gastric resection (two-thirds of stomach removed) and gastro-jejunostomy performed in 1928; since then has developed anemia; undernourished; once pregnant	No free HCl after histamin; peptic activity reduced.
9 . . . (V. McD.)	F	49	Defective diet; "anemic" for years; twice pregnant; overweight	Trace of free HCl after histamin; peptic activity normal.
10 . . .	F	34	Dietary habits fair; four previous pregnancies; four months pregnant; known to have been "anemic" 9 years; underweight	No free HCl after histamin; peptic activity normal.

Observations. Data relative to the important clinical findings and the nature of each individual case are presented in Table 1. It is to be noted that the gastric analyses performed by the same technique on all of the 10 women revealed a complete absence of free hydrochloric acid in the specimens removed after the period of fast and after the alcohol administration. In one of the specimens removed from a patient following the subcutaneous administration of 0.25 mg. of histamin there was a faint trace of free hydrochloric acid, as shown by the slight color change of Töpfer's solution. One other patient showed a low concentration of free acid (15 cc. $\frac{N}{10}$ acid per 100 cc. of gastric juice) after the administration of histamin. Peptic activity of the patients' gastric juice was of high order in all cases. A piece of boiled egg albumen 5 mm. long and 4 mm. in diameter was completely digested in 24 hours. The characteristics, therefore, of the gastric juice in these patients are the absence or greatly diminished amounts of free hydrochloric acid and the presence of pepsin in normal amounts.

The Effect of Large Doses of Iron. Experience in the treatment of hypochromic anemia, as has been previously recorded by various authors,^{4, 7, 14, 18} has shown that patients with this condition respond well to the oral administration of large amounts of various preparations of inorganic iron. The response of the bone-marrow is indicated by the appearance of reticulated (immature) erythrocytes in the circulating blood and by an increase in hemoglobin and number of erythrocytes.

In Table 2 are shown the responses of the hemoglobin and erythrocytes to 6 gm. of iron and ammonium citrate (U. S. P.) fed daily to 3 patients who were permitted to continue taking their regular diet. It is to be noted that the hemoglobin of these patients increased from an average low of 58 per cent to an average high of 88 per cent. It is to be emphasized that the improvement in the state of the blood occurred within a period of 30 days.

TABLE 2.—RESPONSE OF HEMOGLOBIN AND RED BLOOD CELLS TO 6 GM. OF IRON AND AMMONIUM CITRATE DAILY IN PATIENTS WITH DEFECTIVE DIET, GASTRIC ACHLORHYDRIA AND ANEMIA WHILE ON "REGULAR DIET."

Patient No.	Before treatment.*	At 30 days after iron therapy.*	One year after therapy.
1	{ 3.9 46	4.47 96	5.18 89
2	{ 3.27 65	4.59 80	†4.07 73
3	{ 4.2 65	5.3 90	

* Red blood cell count (upper figure); hemoglobin, per cent (lower figure).

† Two years.

The exact duration of the beneficial effect derived from the above therapeutic procedure, once the medication is stopped, is not known.

A remission may be induced and may be expected to persist from a few months to a few years, depending upon the individual case. Relapse is prone to occur after therapy with iron is omitted. Patient 5 had a relapse 4 months after therapy was stopped, and Patient 2 in Table 1 had a similar experience 2 years after she had last received treatment for the anemia. This information concerning the tendency of the anemia to recur is of considerable importance, and would seem to support the idea that the condition may be due to deficient assimilation of iron.

The Ineffectiveness of a Diet Rich in Iron. Table 3 shows a series of determinations of erythrocytes and hemoglobin on a group of patients who were fed a diet rich in iron prior to the administration of large doses of iron. These patients were selected for this experiment because they were intelligent and highly coöperative. It is, of course, imperative in an experiment of this kind that food of the type and amount prescribed be ingested.

TABLE 3.—RESPONSES OF RED BLOOD CELLS AND HEMOGLOBIN TO DIET RICH IN IRON-CONTAINING FOOD, THEN TO 6 GM. OF IRON AND AMMONIUM CITRATE (U. S. P.) IN PATIENTS WITH GASTRIC ACHLORHYDRIA, DEFECTIVE DIET AND ANEMIA.

Patient No.	Before treatment.*	Days after feeding "iron-rich" diet.	Time indicated in previous column.*	At 30 days after iron therapy.*	One year after therapy.
4	4.0	60	3.79	3.89	4.81
	60		55	73	88
6	3.9	53	3.15	4.45	4.64
	55		60	92	92
7	3.5	60	3.5	4.84	4.94
	42		45	80	92

* Red blood cell count (upper figure); hemoglobin, per cent (lower figure).

The diet used in the experiment as an "iron-rich" diet was considered to be adequate in all dietary factors and to contain a large amount of organic iron. The breakfast consisted of 250 cc. of orange juice, 2 soft boiled eggs and 1 piece of toast with butter; the lunch and dinner were each comprised of a combined raw and cooked vegetable salad; 200 gm. of spinach; 200 gm. of beef protein, and, in addition, during at least 1 meal, a dish of apricots, potatoes, a French artichoke and a dish of carrots. This diet is calculated to yield between 16 and 20 mg. of iron daily. It is stated by Sherman²⁰ that a diet containing 10 to 12 mg. of iron daily is more than sufficient to meet the ordinary metabolic demands for iron. This diet, naturally, contains other metallic substances, among which may be mentioned copper and probably magnesium.

These 3 patients who partook of this diet rich in iron had hemoglobin estimations of 60, 55 and 42 per cent at the beginning of the observations and at the end of approximately 60 days the readings were 55, 60 and 45 per cent respectively. This, accordingly, represents no significant change. They apparently were unable to derive

from food the factor or factors essential to the production of hemoglobin.

The determinations of hemoglobin on the same 3 patients, followed throughout the second stage of the experiment, while they were given 6 gm. of iron and ammonium citrate (U. S. P.) daily, show an improvement similar to that induced in the first group of patients. The data presented in Table 3 show the determinations of hemoglobin made prior to therapy with iron, which were 55, 60 and 45 per cent, and again 30 days after treatment was started, wherein there was an increase to 73, 92 and 80 per cent respectively. It will also be noted that an increase in erythrocytes occurred.

It would appear to be shown by this experiment that a diet regarded as fully adequate in content of iron is not alone sufficient to restore the blood in these anemic patients. Only when large doses of iron were administered in addition to the "adequate" diet did they show satisfactory improvement in the blood.

The Rôle of Abnormal Gastric Function. The second important factor demanding investigation was the part played by the achlorhydria or hypochlorhydria in producing the anemia or in preventing its relief by adequate amounts of iron in the diet.

The probable rôle of gastric anacidity in the production of the anemia has been emphasized by various authors.^{12, 13, 14, 15, 16, 17} Achlorhydria may favor the production of anemia, as has been previously suggested by Mettier and Minot.¹⁴ The lack of hydrochloric acid or greatly decreased amounts of it in the stomach could lead to a relative increase of pH in the upper intestine, where iron is largely absorbed, and thus fail to render the contents suitable for assimilation of iron. It was shown in the experiments that iron is absorbed better from an acid than an alkalin or neutral buffered medium.

In the present experiments 4 patients were given a predigested meal over periods of 20 to 42 days. The patients in this group (Cases 5, 8, 9 and 10), all had an anemia of the hypochromic type. They showed on gastric analysis a lack of free hydrochloric acid but the presence of pepsin. Cases 9 and 5 corresponded in general to Faber's description of chronic chlorosis, and Case 8, being similar in type, occurred in a patient following partial gastrectomy, and in Case 10 there was chlorotic anemia of pregnancy.

The meal designated as the predigested meal consisted of 2 soft boiled eggs, 200 gm. of cooked spinach, and 300 gm. of lean beef-protein freed of fibrous tissue.* To this food were added 4 gm. of commercial pepsin and sufficient strong hydrochloric acid to adjust the H-ion concentration to pH3. The mixture was then allowed to digest in the incubator at 37° C. for approximately 6 hours. It was found necessary to adjust this material to pH5 before administra-

* This meal, when ashed and analyzed was found to contain 12.5 mg. of iron.

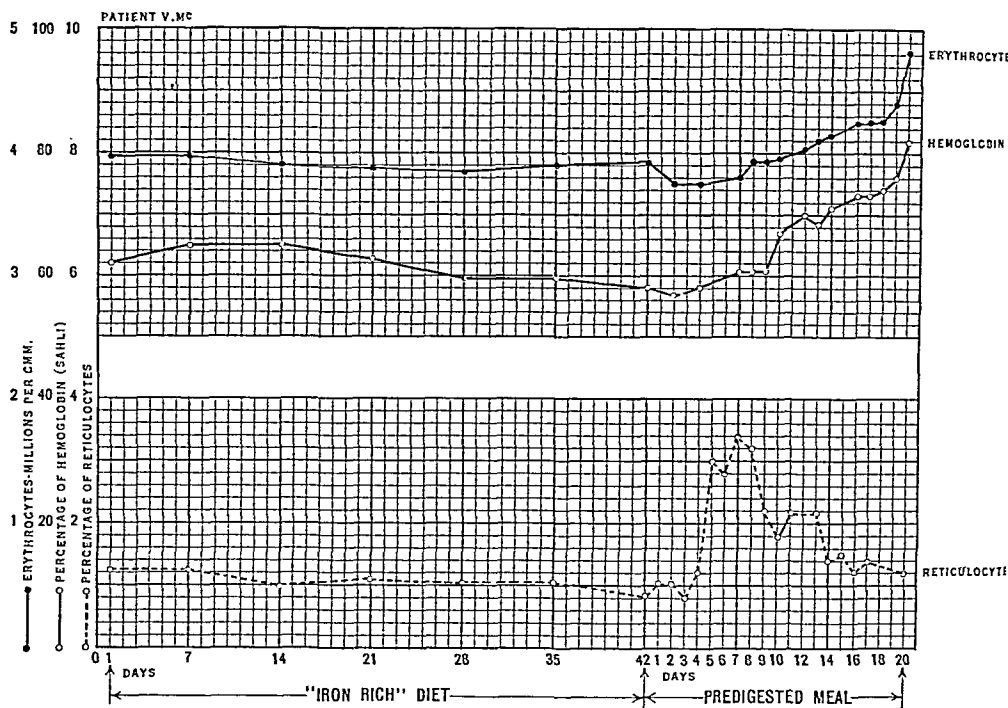


FIG. 1.—The ineffectiveness of an "iron-rich" diet on blood formation in Patient 9, but a satisfactory response to a "predigested" meal.

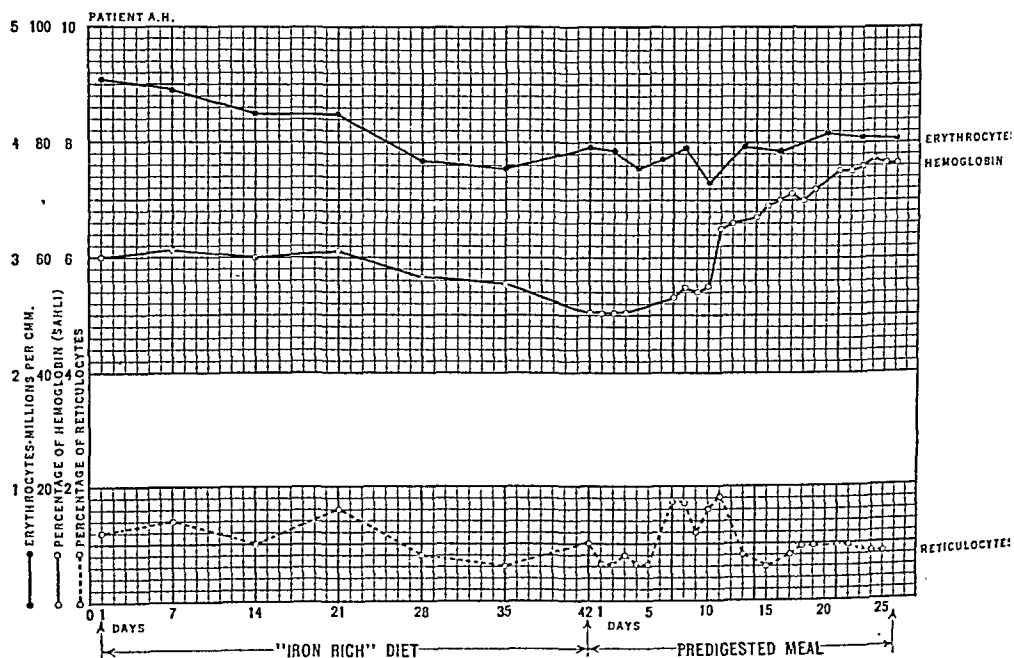


FIG. 2.—The ineffectiveness of an "iron-rich" diet on blood formation in Patient 8 with hypochromic anemia after partial gastrectomy, but a satisfactory response to predigested meals.

tion to the patient to prevent regurgitation. The meal was fed through a tube passed into the stomach. This replaced the evening meal.

As will be seen from an inspection of the data for these 4 patients shown in Figs. 1, 2, 3 and 4, there was a successful reaction to the "predigested meal" as indicated in the course taken by the hemoglobin and erythrocytes. This was in decided contrast to the failure of the blood to increase in numbers of erythrocytes or concentration of hemoglobin during the first period of observation in Patients 8 and 9 (Figs. 1 and 2), while on a diet rich in iron. In addition, it is to be noted that Patient 5 (Fig. 4), following a cessation of therapy with iron, had a relapse in her anemia in spite of the inges-

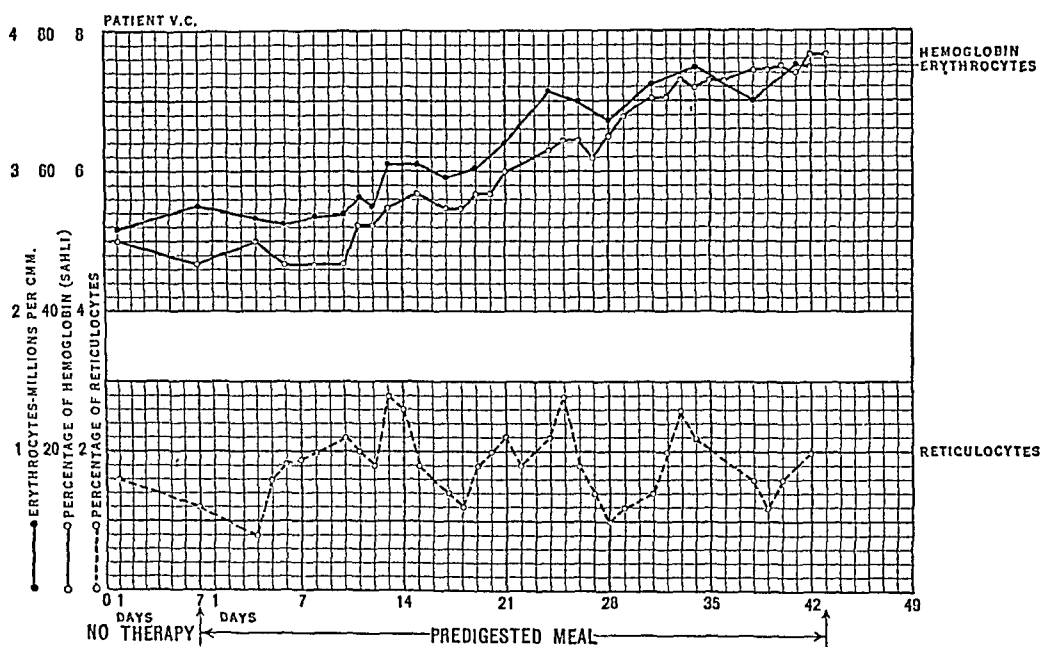


FIG. 3.—The effectiveness of predigested meals on blood formation in Patient 10 with hypochromic anemia of pregnancy.

tion of an iron-rich diet, but the observations made on this patient while being fed the "predigested meal" show a return of the blood toward normal.

It is interesting to note that the increased blood formation is not unlike that occurring in patients following adequate therapy with iron. Within 4 to 6 days after treatment was begun there was a response in the reticulocytes. This response in each case was one of slight degree, but it is to be emphasized that in each instance it was sustained 2 or more days, and was followed soon after by an increase in erythrocytes and hemoglobin. Obviously, one would expect that, since the hypochromic type of anemia is the one under discussion, the improvement in the blood would be chiefly a rise in hemoglobin rather than an increase in the number of cells.

Discussion. The data obtained from the examination of the blood of 10 women with hypochromic anemia associated with gastric hypochlorhydria or achlorhydria serve to illustrate the changes which may take place in erythropoietic activity, depending upon therapy with inorganic iron; the administration of an iron-rich diet, and the feeding of a meal that had been digested *in vitro*. It was clearly demonstrated that patients with hypochromic anemia respond well to suitable therapy with iron, and the results suggest that the defect in the red cells depends upon an abnormality in the metabolism of iron.

Since uncomplicated cases of hypochromic anemia will respond to large doses of iron, the question arises as to whether or not organic iron is as effective as inorganic iron. It has been repeatedly emphasized that large doses of iron are essential to insure a maximum response in the bone marrow, and that small doses have little or no effect unless injected into the subcutaneous or intramuscular tissues.²¹ The administration of a comparable amount of organic iron (in terms of actual content of iron, from the point of view of intake in the diet) is not practical because of the large total mass of food required. However, if the daily requirement of iron is approximately 12 to 15 mg.,²⁰ then it may be assumed that if a similar amount of organic (dietary) iron, *i. e.*, 20 mg., were fed over a long period of time, it should replace the depleted body stores. If, under these circumstances, there is a failure to exhibit absorption of iron as expressed in production of increased percentage of hemoglobin, two possibilities arise to explain this defect: the first, that organic iron is not the factor necessary to hemoglobin production; the second, that iron is not derived from food due to some defect in digestion.

The data of the 3 patients presented in Table 2 and those of the patients recorded in Figs. 1, 2 and 4 indicate that organic (dietary) iron alone is either not available for assimilation or is not absorbed. On the one hand, it does not alleviate the anemia, and on the other, as shown in Fig. 4, it failed to maintain normal kinds and numbers of erythrocytes in the circulating blood. Of the 4 patients who were fed organic (dietary) iron previously acted upon by hydrochloric acid and commercial pepsin, the erythrocytes and hemoglobin returned to within normal limits. A somewhat similar observation has been recorded by Dameshek²² who noted increased formation of red cells in a single case of hypochromic anemia after the administration of a meal digested with normal gastric juice. Assuming, then, that iron is one of the factors essential to erythrocytic production and especially to formation of hemoglobin, the experimental data presented here suggest that we are dealing with a type of deficiency disease wherein there is a failure to digest, assimilate and utilize iron in the food, and that the defective erythropoiesis is dependent upon abnormal digestive function. The altered formation of red cells would seem to be dependent upon the same mechan-

ism, so long as the presence of pepsin occurs in normal amounts, whether it be in patients with uncomplicated simple hypochromic anemia, hypochromic anemia of pregnancy, or in patients with partial gastrectomy.

Summary and Conclusions. Data are presented of studies made on the relationship of diet and nutrition to anemia in 10 cases of chronic idiopathic hypochromic anemia associated with hypochlorhydria or achlorhydria and defective diet.

The response of the bone-marrow, as determined by the hemoglobin and production of erythrocytes, to iron administered in large daily oral doses in the form of iron and ammonium citrate (U. S. P.) was compared to the response in patients on an "iron rich" diet. In addition, a comparison was made of the response of the bone marrow to a diet rich in iron and to a meal previously digested *in vitro* with hydrochloric acid and commercial pepsin.

The bone marrow responded rapidly and excellently to large doses of inorganic iron, but there was no evidence of increased hematopoiesis after the ingestion of an "iron-rich" diet for a long period of time. There was, however, a rapid and satisfactory increase in concentration of hemoglobin, production of red cells, and a slight reticulocyte response following the administration of predigested meals.

It is concluded, from these studies, that chronic idiopathic hypochromic anemia is one presumably due to a deficiency of iron wherein gastric dysfunction leads to failure in utilization of organic (dietary) iron.

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FETAL ENDOMYOCARDITIS: INTRAUTERINE INFECTION AS THE CAUSE OF CONGENITAL CARDIAC ANOMALIES.

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IN the hearts of a number of infants who showed evidences of congenital heart disease at postmortem examination, we have found areas of fibrosis, cellular infiltration and calcium deposition. These changes, we believe, represent the end results of inflammatory processes which, in view of the age of the patients, must have occurred during intrauterine life. Such findings have led us to present the following series of cases with a general discussion of the subject.

Classifications of congenital heart disease usually list the various anomalies under two general headings: (1) those due to primary defective or arrested development, and (2) those due to infection transmitted to the fetus from the mother.

Several factors have been considered as possibilities in the first group. Certain instances are thought to be due to hereditary deficiencies in the germ cells whereby they are predestined to defective development.¹ Evidence for this may be suggested by associated congenital anomalies in other parts of the body. There are also included under this first heading those anomalies which are ascribed to the result of environmental factors which unfavorably influence the development of the growing organ. It has been suggested that chemical, physical or pathologic processes might interfere with the normal development of the heart during the early months when the septa are forming and the heart is assuming its final form. This would give rise to the gross departures from the normal mature form, such as the improper closure of one or more of the septa, anomalous origin of the great vessels, or perhaps one or more of the extreme types of maldevelopment, such as cor triloculare or cor biloculare.

The second group is made up of those instances in which the congenital anomaly is thought to be due to an infectious process involving the heart at some time after the third fetal month when the heart is believed to have assumed its adult form. In these cases the septa are free from defects, the essential relationships of the chambers

and great vessels are normal and the chief abnormalities consist of stenosis or atresia of the valves. It is this latter group of cases which is generally referred to under the heading of "Fetal Endocarditis." It is now generally accepted that myocardial changes are also of importance. This is emphasized by Abbott² who states that "careful investigation of the myocardium in most cases of atresia of the orifices, will reveal patchy yellowish-gray areas visible to the naked eye which microscopically show all stages of degeneration, vacuolation, fatty change and even, in a case under the writer's observation, calcification with cellular infiltration and a diffuse fibrosis which is often myxomatous in character."

Case Reports of Present Group. CASE 1.—C. W., white, male infant, age 36 hours. Cyanosis during last 12 hours. Fetal endomyocarditis; aortic atresia; hypoplasia of left auricle, ventricle, and ascending aorta; calcification of endocardium. Fibrosis of myocardium.

History. Patient was brought to the hospital on September 7, 1932, at the age of 24 hours, because of cyanosis noted for the preceding 7 hours. The mother and father, aged 24 and 27, respectively, were both in good health. Two siblings were in good health. There was no familial history of venereal disease. The essential features in the history are found in Table 2.

The laboratory test of significance here was a negative Wassermann reaction. Death occurred 5 hours after admission, and 36 hours after birth.

*Necropsy** (A-32-149). Performed 12 hours postmortem by Dr. Rew.

Heart. The heart weighed 25 gm. (normal for this age is 17 gm.). In the atrioventricular sulcus, and along the pulmonary artery and aorta were several small petechial hemorrhages beneath the epicardium. The right auricle was greatly distended. The pulmonary artery was much larger than normal. The aorta arose from a normal situation and gave off branches in the usual manner. However, the portion of it lying between the aortic orifice and the junction with the ductus arteriosus was small and cordlike with a marked decrease in its caliber. The ductus arteriosus was still patent, measuring about 6 mm. in length and about 6 mm. in diameter. The chambers of the right side showed nothing abnormal except dilatation and slight hypertrophy. The pulmonary valve measured 26 mm., and the tricuspid valve 48 mm. in circumference. The right ventricular wall measured 3 mm. in thickness. The left auricle was represented by a very small slitlike pocket measuring about 8 mm. in length. The mitral valve was stenosed and possessed thickened, partially fused cusps. It measured 12 mm. in circumference. The left ventricle was also a very small chamber measuring about 1.5 cm. in its longest axis, and 0.5 cm. in diameter. Its inner surface consisted of a thick, dirty white layer of endocardium about 2 mm. in thickness. The chordæ tendineæ were short and thick. The papillary muscles were indistinguishable. There was a complete atresia of the aortic orifice which was represented by a small pit where the aortic valve should be. The left ventricular myocardium which measured 6 mm. in thickness was of normal color, firm in consistency, and free from any evidence of scarring, inflammation or infarction. The right coronary artery appeared normal; the left was not located grossly. It was found only as serial sections were made through the point of atresia.

* In each case a complete necropsy was performed. Only the findings in the heart are described in detail. Other pathologic features are briefly summarized. No evidence of syphilis was found in the general viscera. Congenital malformations were limited to the heart.

Sections for microscopic study were taken from the wall of the right ventricle, including the tricuspid valve and a portion of the auricular wall; other sections were taken transversely across the left ventricle; serial sections were taken through the point of atresia of the aortic orifice. These were stained with hematoxylin and eosin, phosphotungstic acid with hematoxylin, aniline blue, and with Scharlach R for fat. The most outstanding feature of these sections was the enormous thickening and fibrosis of the endocardium of the left ventricle. Extending deep into the myocardium from the endocardium were bundles and tongues of connective tissue. The myocardium underlying this thickened endocardium showed degenerative changes in the muscle bundles, consisting of finely divided fat droplets dispersed throughout the muscle fibers. Nowhere was there cellular infiltration. Serial sections cut through the point of atresia showed small areas of calcification surrounded by cicatricial tissue. Von Kossa stains of these areas proved definitely the presence of calcium. The section from the right heart showed nothing unusual. *Further pathologic findings:* Terminal aspiration pneumonia; disseminated petechial hemorrhages; generalized vascular congestion.

CASE 2.—A. L., white male infant, aged $2\frac{1}{2}$ months. Mother had "flu" during pregnancy. Cyanosis and convulsions since birth. Endocarditis (healed), cardiac hypertrophy.

History. The patient was brought to the hospital on October 9, 1932, because of "blueness," "failure to gain," and convulsive seizure since birth. (See Table 2.) Wassermann reaction was negative.

Necropsy (A-31-153) by Dr. Gross.

Mediastinum. Examination of the aortic arch showed an anomaly in that the right innominate and left common carotid artery arose together from the aortic arch.

Heart. The heart showed generalized hypertrophy. It weighed 70 gm. (normal weight for this age is 23 gm.). The hypertrophy was most marked in the chambers of the left side. The wall of the left ventricle measured 10 mm. in thickness; of the left auricle 3 mm. The aortic valve which measured 16 mm. in circumference, was stenosed, with thickened, partially fused cusps. Attached to the margins of the cusps were several small fibrous nodules. The mitral ring measured 32 mm. in circumference. Its valve leaflets showed no gross abnormalities. The endocardium covering the papillary muscles on the left was yellowish, thickened and sclerosed. The endocardium of the left auricle also showed a patchy distribution of yellowish thickening. The papillary musculature was scarred and suggested calcification. Elsewhere the myocardium showed no gross changes. The right side of the heart showed only a generalized hypertrophy. The right ventricular myocardium measured 6 to 7 mm. in thickness. The pulmonary and tricuspid valves appeared normal, measuring 24 mm. and 38 mm. respectively. The ductus arteriosus was patent, admitting a 2-mm. probe. The coronary arteries appeared normal.

Sections for microscopic study were taken from the wall of the left ventricle, the scarred papillary muscles, the mitral and aortic valves. These were stained with hematoxylin and eosin, phosphotungstic acid with hematoxylin, von Kossa's stain for calcium, and Scharlach R for fat. The myocardium of the papillary muscle and left ventricular wall showed the most interesting changes. There were many prominent scars consisting of dense connective tissue. There was a considerable amount of separation and hyalinization of the muscle fibrils with a slight, diffuse, cellular infiltration. The endocardium of the papillary muscle was thickened and fibrosed with a diffuse cellular infiltration. The underlying musculature was extensively scarred and showed small scattered areas of calcification. The sections of the aortic and mitral valves showed a generalized thickening, hyalinization and slight degree of cellular infiltration.

Further Pathologic Findings. Terminal bronchopneumonia, generalized passive congestion.

CASE 3.—L. C., male infant, aged 5 months, heart murmurs since birth, cyanosis, streptococcus hemolyticus septicemia. Pulmonary stenosis.

History. The patient was brought to this hospital for the first time on August 25, 1931, because of swelling of the right thigh and failure to move the right leg.

The mother of the patient had suffered since childhood from "heart trouble" which was presumably of a rheumatic type. She was very ill during this pregnancy with dyspnea, high blood pressure, nausea and vomiting. The first child was in good health; the second had anemia; the 3d pregnancy resulted in a miscarriage, the patient represented the 4th pregnancy. After the 3d pregnancy she was told she should not have any more children because of a "bad heart." The patient was born at full term by a normal easy delivery. The birth weight was 4 pounds 11 ounces. A diagnosis of congenital heart disease was made because of a loud blowing systolic murmur heard immediately after birth. Cyanosis was first noted at the age of 1 month. At this time the heart was slightly enlarged by teleoroentgenograms.

Death followed a streptococcus hemolyticus septicemia. The blood Wassermann reaction was negative. Teleoroentgenograms showed a normal heart shadow which was not enlarged for this age. The lung folds were clear.

Necropsy (A-31-132).

Heart. The heart weighed 30 gm. (normal weight for this age is 29 gm.). The left side of the heart showed no gross abnormalities. The mitral valve measured 34 mm. in circumference; the aortic 25 mm. The wall of the left ventricle was 8 mm. in thickness. The foramen ovale and ductus arteriosus were both closed. There were no septal defects. The aorta arose from a normal situation. The coronary arteries appeared normal. The branches of the aorta were anomalous in that the left common carotid and left subclavian both arose separately from the aortic arch.

The right auricle was slightly dilated, the right ventricle was dilated and hypertrophied. The right ventricular wall measured 7 mm. in thickness as contrasted with 2 to 3 mm. as the expected normal for this age. The tricuspid valve, which measured 32 mm. in circumference appeared entirely normal. The most important pathologic changes were found in the pulmonary valve which was stenosed, measuring 16 mm. in circumference. The cusps were thickened with opaque, yellowish, roughened surfaces. On the superior surface of the anterior leaflet was a fresh fibrinous vegetation, firmly attached to the valve surface measuring about 1.5 mm. in diameter. No further vegetations or thrombi were found elsewhere in the heart. The right ventricular wall was 7 mm. in thickness, as contrasted with 2 to 3 mm. as the expected normal for this age, and 8 mm. for the left ventricular wall. The myocardium was of a uniform reddish color with no gross evidence of fibrosis, degenerative or inflammatory changes.

Sections for microscopic study were taken from the left ventricular including the mitral valve, and from the right ventricular wall including the pulmonary valve with its vegetation. Diffusely scattered through the myocardium of both the right and left chambers were small, focal clusters of densely packed streptococci. No evidence of fibrosis was found in the myocardium. The pulmonary valve was thickened with a definite increase in the connective tissue elements. On its arterial surface was a small vegetation consisting of densely packed streptococci. The findings here represent old damage to the pulmonary valve with a superimposed fresh inflammatory process.

Further Pathologic Findings. Osteomyelitis of the right femur; bronchopneumonia; acute intracapillary glomerular nephritis.

CASE 4.—W. N., white male infant, aged 3 days, cyanosis and dyspnea since birth. Healed endocarditis with mitral and aortic stenosis.

History. The patient's birth was attended by the outpatient department of the Boston Lying-in Hospital. He was brought there January 22, 1931, on the 3d day of life because of cyanosis, dyspnea, and failure to nurse.

This was the 4th pregnancy of the mother, aged 32, who was in apparent good health at the time of delivery. Her family history and past history were entirely negative. Her first two children were normal and healthy. The 3d pregnancy was interrupted by a spontaneous miscarriage at the 5th month. During this pregnancy her course was normal except for a mild cold 2 weeks before term.

Death occurred several hours after entry.

Necropsy (A-32-94)*.

Heart. The heart weighed 28 gm. (normal for this age is 17 gm.). The right auricle and right ventricle were hypertrophied and moderately dilated, but otherwise not unusual. The right ventricular myocardium measured 4 to 5 mm. in thickness. The endocardium appeared normal. The pulmonary and tricuspid valves were also moderately dilated, measuring 2.7 cm. and 4 cm. in circumference. The chambers of the left side were much smaller than normal. The volume of the left ventricle was estimated at slightly less than 1 cc. Its myocardial wall measured 7 to 8 mm. in thickness and was somewhat less firm, but of the same color as the normal looking right ventricular myocardium. There were no areas of softening or fibrosis. Both aortic and mitral valves were markedly stenosed; neither admitted more than a 2-mm. probe. The cusps and leaflets of these valves were smooth, thickened, partially fused and free from vegetations. The entire endocardium of the left ventricle was yellowish in appearance and showed a diffuse and unusual degree of thickening. The chordae tendineae were involved in the same process, being thickened and shortened. The papillary muscles were indistinguishable as such, being obliterated by the cicatrization. The ductus arteriosus was markedly dilated, measuring 46 mm. in diameter. The foramen ovale appeared normal; it was patent with a valve covering $\frac{2}{4}$ of the opening, the latter being 2 to 3 mm. in diameter. The coronary arteries were normal.

Sections for microscopic study were taken from various portions of the walls of the four chambers, and from the mitral valve. These were stained with hematoxylin and eosin, eosin methylene blue, aniline blue, phosphotungstic acid with hematoxylin, and for fat with Scharlach R and hematoxylin. The most significant feature of these sections was the extreme thickness of the endocardium lining all surfaces of the left side of the heart. This was most evident in the endocardium of the left ventricle. Here the endocardial layer measured 1 mm. in thickness in contrast to the myocardium which averaged 3 mm. in thickness. The endocardium in these sections was even and regular, showing nothing abnormal except the generalized thickening. No irregular strands of connective tissue, cellular infiltration or increased vascularity were seen anywhere in the endocardium or myocardium. Sections of the mitral valve showed essentially the same features with a generalized thickening and hypertrophy of the connective tissue elements with no evidence of increased vascularity or cellular infiltration. The valvular endocardial surfaces were all smooth and regular, showing no evidence of either past or present vegetations.

Discussion. We have collected from the literature 10 cases to which we have added 4 of our own, making a total of 14, in all of which there is evidence indicating that the cardiac changes can best be explained on the basis of an infectious process originating

* Dr. A. T. Hertig kindly supplied the material for study in this case.

TABLE 1.—CASES OF FETAL ENDOMYOCARDITIS IN THE LITERATURE.

Serial No.	Source.	Age.	Mother's pregnancy.	Symptoms.	Valvular defect.	Associated pathologic changes (gross).	Histopathology.
1	Stinasny ³	4 days	Not significant	Cyanosis—sudden death	Aortic stenosis	Endocardium of left ventricle thickened	Myocardial fibrosis and vacuolation.
2	Jacobsthal ⁴	3 weeks	None	Calcification, right papillary muscle	Calcium deposition.
3	Ruge ⁵	Premature	Aortic atresia	Hypoplasia of left vent. and aorta; endocardium of left vent. thickened	Myocardial fibrosis.
4	Monteberg ⁶	4 days	Mother reported well	Cyanosis, dyspnea, sudden death	Aortic stenosis	Endocardium of left vent. thickened	Endocardial and myocardial fibrosis.
5	Kockel ⁷	4 hours	Bronchitis 2 months before delivery	Aortic stenosis; mitral stenosis	Endocardium of left vent. thickened	Endocardial fibrosis; myocardial degen. and calcif.
6	Ganoff ⁸	1½ hours	Diarrhea in 8th mo.	No cyanosis	Mitral insufficiency	"Verrucous endocarditis;" fibrous myocarditis.
7	Fischer ⁹	5 weeks	"Influenza" 6 weeks before delivery	Cyanosis; edema of arms and legs	Aortic stenosis; mitral stenosis	Hypert. of both vent.; endocardium of left vent. thickened	Acute and chr. myocarditis with scarring and calcif.
8	Loeser ¹⁰	40 hours	Mother reported well	Cyanosis; dyspnea	Aortic atresia	Hypert. of right vent.; hypoplasia of left vent. and aorta; endocardium of left vent. thickened	Endocardial thickening.
9	Von Zalkau	2 days	Not reported	Pulmonary atresia; tricuspid stenosis	Hypert. of right vent.	Myocardial fibrosis.
10	Bellet and Gouley ¹¹	12 hours	Aortic atresia	Hypoplasia of left heart; myocardial scar	Myocardial scar.

TABLE 2.—AUTHORS' SERIES.

Age.	Mother's pregnancy.	Symptoms.	Heart signs.	Valvular defect.	Associated pathologic changes (gross).	Histopathology.
C. W. 5 mos.	Mother a cardiac patient	Terminal cough; edema and cyanosis	None	Aortic atresia	Hypoplasia of left auricle, vent. and aorta; endocardial thickening of left vent.	Endocardial fibrosis; myocardial fibrosis and calcif.
A. L. 2½ mos.	Mother confined to bed with the "flu" before term	Cyanosis; increasing convulsions	Heart enlarged; systolic thrill and diastolic murmur heard best at base	Aortic stenosis	Endocardial thickening of left vent. and auricle	Cellular infiltr. fibrosis and calcif. of myocardium.
L. C. 5 mos.	Mother a cardiac patient	Terminal cough; edema and cyanosis	Heart not enlarged; thrill and loud systolic apical murmur	Pulmonary stenosis	Secondary terminal acute streptococcus endocarditis	Old healed endocarditis and acute endocarditis and myocarditis.
W. N. 3 days	Two weeks before delivery confined to bed with a cold	Cyanosis; edema	None	Aortic stenosis; mitral stenosis	Hypoplasia and endocardial thickening of left auricle and vent.	Thickening of endocardium.

in intrauterine life. We have included in this series only those cases occurring in earliest infancy in which the gross pathologic findings have been supported by microscopic studies of sufficient adequacy to make them convincing. The cases selected from the literature are summarized in Table 1.

In the instances gathered from the literature, 8 died within the first 4 days of life. Of our own cases 2 died within the first 3 days, 1 lived $2\frac{1}{2}$ months and the other 5 months. In the 2 latter cases there was clinical evidence of heart disease since birth. One had cyanosis since birth; congenital heart disease was recognized in the other because of a heart murmur heard since birth.

Knowledge concerning the health of the mother during pregnancy is inadequate. In 4 of the 10 cases from the literature, there is no information concerning the mother's health. In 2, the mother was reported well during pregnancy. One mother contracted bronchitis 2 months before delivery; another was sick with "influenza" 6 weeks before delivery.

In the present group one mother was entirely normal throughout the term of her pregnancy as far as we could learn. Another was a known cardiac patient but suffered no acute infection during her pregnancy. The mother of one contracted a mild upper respiratory infection of sufficient severity to confine her to bed 2 weeks before term. Another was ill with what was called "flu" 2 months before term. In only 2 of our group therefore was there any definite acute illness in the mother during pregnancy. These, together with 2 from the literature make a total of 4 in which there was a history of bronchitis, "influenza," or upper respiratory infection.

In regard to symptomatology, the most frequent finding throughout the series is cyanosis. Dyspnea and peripheral edema and other evidence of cardiac damage were found less frequently. Death often occurred unexpectedly.

Physical signs on examination of the heart which might indicate cardiac disease were not found in any of the instances in the literature. In our own group a murmur was heard in only 2 and only once was the heart enlarged to percussion. In the other 2 cases the hearts were clinically recorded as normal.

In regard to the pathologic features it is of importance here to emphasize only the findings indicating that in these cases the cardiac abnormalities represent the end results of old inflammatory processes. Of these findings, the most important are: (1) the gross distortion of the valves and the thickening of the endocardial surfaces, and (2) the microscopic evidence of previous infection, such as fibrosis and calcification.

Considering first the gross features, there was aortic stenosis in 7 of the total series. Five of these also showed changes in the mitral valve. One had pulmonary stenosis with a superimposed terminal acute bacterial endocarditis. In all the instances of steno-

sis, the appearance of the leaflets resembled the changes found in chronic valvular disease of later life. Aortic atresia occurred 4 times and pulmonary atresia once. In only 1 case were all the valves recorded as normal (Jacobsthal), but there was scarring and calcification of the myocardium. Associated with the primary valvular defects there may be secondary changes of varying degree. With aortic atresia, such changes are marked. The left ventricle serves merely as a functionless blind pocket communicating only with the left auricle. It is found to be small and hypoplastic. Similarly, the function of the aorta is only to carry blood to the coronaries by retrograde flow from the ductus arteriosus. Thus the aorta, too, is a hypoplastic structure. When the aortic orifice is narrowed rather than completely obliterated, the left ventricle is found larger than normal. In but 2 (1 of aortic atresia and 1 of aortic stenosis), although the endocardium was greatly thickened, the myocardium failed to show pathologic changes. In 4 cases calcium deposits were found in the myocardium. In 3, 2 from the literature and 1 of our own, the calcification was limited to papillary muscles of the left ventricle. In our case of aortic atresia the calcification was revealed only by making serial sections through the point of atresia.

In regard to calcification of the myocardium, there are 2 cases which deserve brief mention here. The first is a case recently reported by Diamond.¹³ A mother who had been in good health was delivered during the 7th month of pregnancy of an infant, who died 30 minutes after birth. At necropsy extensive calcification was found in the right auricle and throughout the myocardium of both ventricles. The author ascribed this to the result of a "toxic necrosis of the myocardium" transmitted from the mother. We have observed an infant who was born normally of healthy parents, and who, on the 2d day, developed cyanosis and dyspnea. Death occurred on the 4th day. At necropsy a calcified mass was revealed, almost completely occluding the tricuspid orifice. Atheromatous changes were found in the coronary arteries. Such cases may properly belong in the category of fetal endomyocarditis. However, until more is known about the nature of these and similar cases, their pathogenesis must remain uncertain.

In considering the etiologic possibilities it is important to exclude congenital syphilis. In the cases from the literature, syphilis has been definitely excluded in those reported by Mönkeberg, Loeser and Bellet and Gouley. In the remaining cases from the literature, exclusion must rest upon two factors: (1) the absence of other evidence of congenital syphilis in the body and (2) the nature of the cardiac lesion. Warthin¹⁴ has shown that the prevailing lesion of congenital syphilis of the heart is a fibrous myocarditis harboring colonies of spirochetes. In the instances of congenital syphilis of the heart which we have encountered in the literature or in our



FIG. 1.—Photograph of heart in Case 4, showing left ventricle and aortic valve.
Note greatly thickened endocardium and chordæ tendinæ.

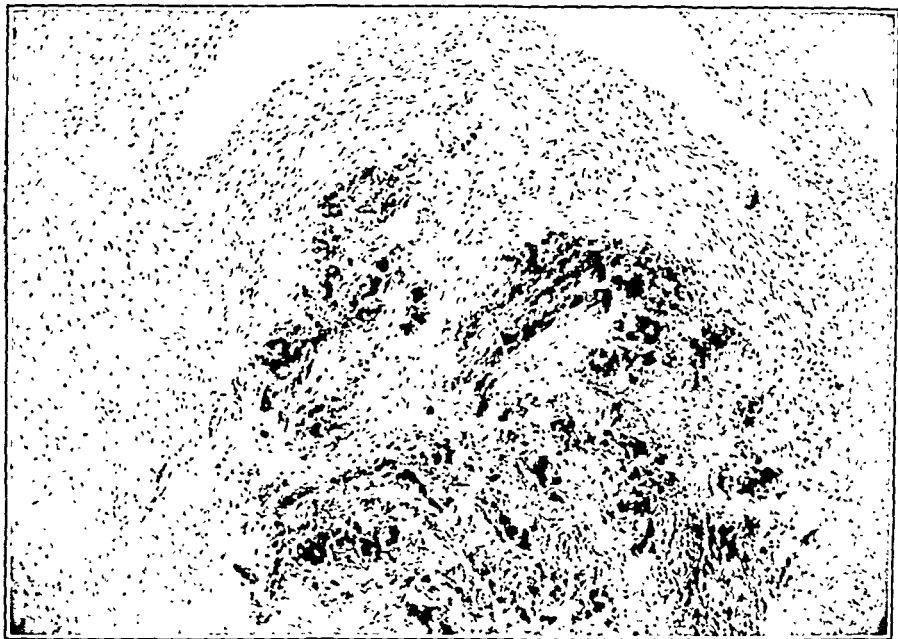


FIG. 2.—Photomicrograph of section through scarred area at base of aortic valve in Case 1, showing heavy deposits of calcium. Note lumen of aorta above. (Hematoxylin and eosin $\times 104$.)



FIG. 3.—Photomicrograph of section through myocardium of left ventricle in Case 2. Note fibrosis in myocardium. (Hematoxylin and eosin $\times 118$.)

laboratory, valvular lesions are conspicuously absent. In the series presented here, valvular stenosis and atresia are the prevailing lesions. Further negative evidence is furnished in our own group by the negative history of syphilis in the parents and negative Wassermann reactions obtained from the infant in each instance.

Of the nature of the infection in this series of patients or its mode of transmission we know little. In a few instances in this series, the mother contracted an "influenza" type of infection in the 7th or 8th month of pregnancy. It has been claimed that this was responsible for the cardiac changes in the infant. However, we know too little of the nature of such infections to be able to consider such a view as more than a stimulating suggestion.

It would appear profitable, as soon as a diagnosis of congenital heart disease is suspected, to make a careful review of the health of the mother during pregnancy, with particular emphasis on the nature, severity and time of occurrence of any acute infection. By this means information can be collected which may lead to an understanding of one of the causes of permanent and irreparable cardiac damage in the newborn.

Summary. 1. Fetal endomyocarditis as one of the causes of congenital heart disease is discussed.

2. A summary is given of 10 cases collected from the literature and 4 of our own, all free from evidences of congenital syphilis.

3. In each of the total series of 14 there is gross and microscopic evidence pointing to old infection. In view of the early death of each infant the infectious process must have occurred during intra-uterine life. The nature of the infection is uncertain.

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RIGHT VENTRICULAR PREPONDERANCE (AXIS DEVIATION) OF THE HEART. THE SIGNIFICANCE OF VENTRICULAR PREPONDERANCE AND T-WAVE INVERSION IN THE HUMAN ELECTROCARDIOGRAM.

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At the New York Hospital and the Cornell Clinic the electrocardiograms of the last 4 years showing a right ventricular preponderance of the *Q-R-S* group were studied. This was done because it was thought that this type of electrical tracing would lead to observations on the right-sided enlargement of the heart. In 1929, attention¹ was directed to the electrocardiogram in arterial hypertension, a condition in which there is essentially left-sided enlargement. In summary, the record in arterial hypertension consisted of a left ventricular preponderance, or a left ventricular preponderance with T_1 inversion. It was concluded that these electrocardiograms were associated with an enlarged hypertrophied left ventricle and that the T_1 inversion was due to this anatomic change and not due to disease of the coronary arteries. It is thought that right ventricular preponderance alone, but more usually with T_3 or T_{2-3} inversion is a result of, or associated with, right-sided enlargement of the heart.*

The patients examined in this investigation had not received any digitalis at all or else the electrocardiograms were taken when digitalis had not been given for some time. Furthermore, the T-wave inversions were permanent abnormalities.

Among the 173 cases exhibiting right ventricular preponderance there were 99 (57 per cent) in which there was chronic rheumatic valvular disease (Table 1). In 7 of these 99 cases no specific valvular lesions were enumerated on the hospital charts, but in the remaining 92 cases mitral stenosis was present in each instance, either alone or associated with other lesions. In not a single case was aortic insufficiency the sole valvular lesion.

The degenerative type of heart disease composed the second largest group (Table 1). In this group there were 36 patients (21 per cent) who suffered from the following diseases: myocardial degeneration (11), arteriosclerosis (14), sclerosis or thrombosis of the coronary artery (7), hypertension (4).

* An interpretation of right ventricular preponderance was made when the main downward deflection in Lead I, that is to say, the S wave, was deeper than in either of the other two leads and the main upward deflection in Lead III (R wave) was taller than in either of the other two leads.

TABLE 1.—RIGHT VENTRICULAR PREPONDERANCE (173 CASES).

Diagnosis.	T-wave inversion.	No.	Per cent.	Sex.		Roentgenogram.				Electrocardiogram.			
				M.	F.	Dead.	Enlarged heart.	Left auricle and pulm. conus.	Lung markings and congestion.	X-ray missing.	Auricular fibrillation.	Changes P-waves.	Changes Q-R-S.
Chronic valvular disease	None	19	19	10	9	3 (16%)	8 (42%)	8 (42%)	7 (37%)	2	2 (10½%)	6 (32%)	4 (21%)
	T ₂ and T ₃	29	29	13	16	7 (24%)	14 (46%)	13 (45%)	13 (45%)	6	6 (21%)	9 (32%)	12 (41%)
	T ₂ and T ₃	48	48	20	28	18 (37%)	34 (71%)	27 (56%)	30 (62½%)	10	25 (52%)	15 (31%)	21 (44%)
	Misc.	3	3	1	2	0	1	0	2	0	3	1	1
	Total	99	57	44	55	28 (28%)	57 (58%)	48 (48%)	52 (53%)	18	36 (36%)	31 (31%)	38 (38%)
Degenerative heart* disease	None	10	28	8	2	0	3	0	4	2	1	1	4
	T ₂ and T ₃	6	17	5	1	0	0	0	2	3	0	1	4
	T ₂ and T ₃	18	50	11	7	7	9	1	11	7	6	1	10
	Misc.	2	6	2	0	0	0	0	0	2	0	0	1
	Total	36	21	26	10	7	12	1	17	14	7	3	19
Congenital	Total	3	2	2	1	0	1	0	0	0	1	1	1
	Total	3	2	3	0	0	1	0	0	1	1	1	1
Non-cardiac†	None	12	38	11	1	0	0	0	1	2	0	2	1
	T ₂ and T ₃	9	28	6	3	0	0	2	2	2	0	3	3
	T ₂ and T ₃	10	31	2	8	1	0	3	3	1	0	1	3
	Misc.	1	3	0	1	1	0	0	0	1	0	0	0
	Total	32	19	19	13	2	0	5	6	6	0	6	7
	Total	173											

* Myocardial degeneration (11), arteriosclerosis (14), coronary artery sclerosis or thrombosis (7), hypertension (4), singly in or combinations.
 † Thyroid disease (7), emphysema, bronchial asthma or bronchitis (6), chronic tonsillitis (6), lobar pneumonia (2), tuberculosis of peritoneum (1), pleurisy (1), miscellaneous (9).

The 32 primarily non-cardiac cases consisted of 7 suffering from thyroid disease, 6 from emphysema, bronchial asthma, or bronchitis, 6 from chronic tonsillitis, 2 from lobar pneumonia, 1 from tuberculous peritonitis, 1 from pleurisy and finally 9 cases in which definite diagnoses were not made.

There were 3 cases of congenital heart disease and 3 cases of syphilis.

TABLE 2.—SUMMARY OF RIGHT VENTRICULAR PREPONDERANCE CASES.

T-wave inversions.	No.	Per cent.	Sex.		Dead.	Enlarged heart.	Left auricle, pulm. conus.	Increased vascular shadows.	X-ray missing.	Auricular fibrillation.	P-wave.	Q-R-S.
			M.	F.								
None	41	24	29	12	3 (7%)	11 (27%)	8 (20%)	12 (29%)	6 (15%)	3 (7%)	9 (22%)	9 (22%)
T ₁ only	47	27	27	20	7 (15%)	16 (34%)	15 (32%)	17 (36%)	11 (23%)	8 (17%)	13 (28%)	21 (45%)
T ₂ and T ₃	78	45	34	44	26 (33%)	43 (55%)	31 (40%)	44 (56%)	18 (23%)	31 (40%)	18 (23%)	34 (44%)
(Misc.)	7	4	4	3	1	1	0	2	4	3	2	2
Total	173		94	79	37 (21%)	71 (41%)	54 (31%)	75 (43%)	39 (23%)	45 (26%)	42 (24%)	66 (38%)

A survey of the data obtained from the patients showing right ventricular preponderance (Table 1 and Figs. 1, 2, 3) yields information of clinical significance. Female subjects were more numerous in the group with chronic rheumatic valvular disease, but male individuals were in the majority in the cases with degenerative heart disease. All the cases have been subdivided into three divisions from an electrocardiographic point of view; those with no T-wave inversion, those with T-wave inversion in Lead III only, and finally, those with T-wave inversion in both Leads II and III. The summary will be analyzed in detail (Table 2). Of 41 patients with no inversion of the T-wave, only 7 per cent died, 27 per cent had enlarged hearts on the teleroentgenograms, 20 per cent showed a prominence in the region of the pulmonary conus and the left auricle, 29 per cent exhibited increased lung markings with suggestive vascular changes in the pulmonary vessels, 7 per cent exhibited auricular fibrillation, and 22 per cent showed Q-R-S abnormalities. In the next group with T₃ inversion alone, all the numbers became greater, that is to say, the mortality increased to 15 per cent, enlarged hearts to 34 per cent, bulge in the pulmonary conus region to 32 per cent, pulmonary vessel changes to 36 per cent, auricular fibrillation to 17 per cent, Q-R-S findings to 45 per cent. In the third subdivision (the cases with T₂₋₃ inversions together) these numbers reach their maximum: Mortality 33 per cent, enlarged hearts 55 per cent, prominence of pulmonary conus 40 per cent, increased lung markings 56 per cent, auricular fibrillation 40 per cent, Q-R-S abnormalities 44 per cent. The conclusions to be drawn from these enumerations are these. Right ventricular preponderance with inversion of the T-waves in Leads II and III

is associated with the largest hearts, with the most frequent and most prominent bulge in the region of the left auricle and pulmonary conus, and with the greatest increase in tension in the pulmonary circuit. Clinically, it is the most serious lesion as shown by highest mortality rate and by high incidence of auricular fibrillation and *Q-R-S* changes. Next in severity is the right ventricular preponderance with only T_3 inversion and least in severity is the patient with right ventricular preponderance without any inversion of the T-wave.

An analysis of the findings in the patients who died reveals facts that are in harmony with the correlations previously made (Table 3). In the electrocardiograms of 37 patients who died the T-wave was inverted in Leads II and III in 32 cases, in Lead II alone 4 times only and the T-wave was upright in all leads only once. In other words, an overwhelming proportion of the patients who died exhibited inversion of T-waves in Leads II and III together. The Roentgen ray films emphasize the fact that these patients had enlarged hearts with prominence of the pulmonary conus.

TABLE 3.—FATAL CASES WITH RIGHT VENTRICULAR PREPONDERANCE.

	No.	Per cent.	Increased size heart.	Pulmonary conus.	Increased lung markings.	Mitral valve lesion.	Aortic valve lesion.	T-wave inversions.			Auricular fibrillation.	P-wave.	Changes Q-R-S.
								None.	T_2 only.	T_2 and T_3 .			
No autopsy . . .	24*	65	19	14	19	16	5	1	2	21	11	5	14
Autopsy . . .	13	35	12	10	12	11	6	0	2	11	3	3	5
Total . . .	37		31	24	31	27	11	1	4	32	14	8	19

* No Roentgen ray picture in 5 patients.

The 45 patients suffering from auricular fibrillation showed many points of clinical importance. The mortality rate in this group was $33\frac{1}{3}$ per cent, whereas the general mortality rate was 21 per cent. All the patients with auricular fibrillation under 50 years of age had a mitral stenosis. In short, a patient under 50 years of age showing a right ventricular preponderance and also auricular fibrillation, even though a diastolic murmur is not present, has in all likelihood mitral stenosis and the etiologic factor is probably rheumatic.

The frequency of abnormalities of the P-waves (31 per cent in the valvular disease cases) is to be attributed to the auricular hypertrophy, the result of mitral stenosis. The incidence of auricular hypertrophy may even be greater, since one-fourth of this group suffered from auricular fibrillation, a condition in which P-waves in the electrocardiogram disappear.

Discussion. In a survey of 235 normal adults (over 20 years of age) who were thoroughly examined at the Cornell University

Medical College during the last 5 years a right ventricular preponderance in the electrocardiogram was found only 3 times. This occurred in individuals with small or drop hearts. It is apparent that this electrocardiographic change should suggest that an abnormal or pathologic condition is present in the heart unless the heart in question is hypoplastic or pendulous.

It is clear that the electrocardiographic changes of right ventricular preponderance, right ventricular preponderance with T_3 inversion, or with T_{2-3} inversions, are closely related to the shape and size of the ventricles of the heart, particularly in reference to each other and with regard, of course, to the frontal plane of the body, the plane in which the electrocardiogram is led off. As the right ventricle enlarges, it makes up more and more of the anterior surface of the heart. Many factors come into play. Whether the conduction pathways in the right ventricle and pulmonary conus are lengthened and the muscle walls thickened, or their position changes, or the rate of passage of the excitation wave decreases, or the onset or the end of electrical excitation in the two ventricles is altered or whether a combination of any or all of these factors occurs, it appears that it is not primarily the anatomic condition of the heart muscle cell but rather the relation of the conduction pathways in the chambers which is important in the establishment of a right ventricular preponderance with T-wave inversion. Another bit of evidence to strengthen this view that the important factor is the position and shape of the heart chambers rather than the condition of the muscle fiber is the fact that of the 13 patients upon whom an autopsy was performed there were 3 in whom no evidence of myocardial damage was found on gross examination or microscopically and only 1 of the 13 had disease of the coronary vessels.

In the 13 postmortem examinations 12 very large hearts were found and in 10 cases the right ventricle was described as relatively more enlarged and hypertrophied than the left. This emphasis on right ventricular enlargement strengthens the belief that right ventricular preponderance with inversion of T_3 alone or both T_2 and T_3 is characteristic of right ventricular enlargement.

A great deal of clinical and experimental evidence has accumulated which substantiates the views which have just been expressed. Willius² found that preponderance of the left ventricle was often associated with negativity of the T-wave in Lead I or in Leads I and II, and right-sided preponderance with negativity of T_{2-3} and next with T_3 . Barnes and Whitten³ observed that in predominant left ventricular strain T_1 or T_{1-2} were inverted and in predominant right ventricular strain, T_{2-3} . From experiments also, similar facts are present. Using the heart-lung preparation Daly⁴ found T_1 negative when excessive strain was placed on the left heart, that is to say, when the left ventricle performed work in excess (relative to the normal heart) of that of the right ventricle. In two experi-

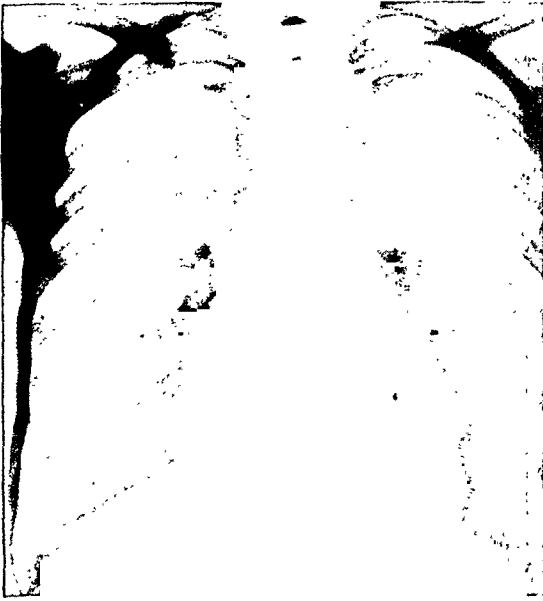


FIG. 1a

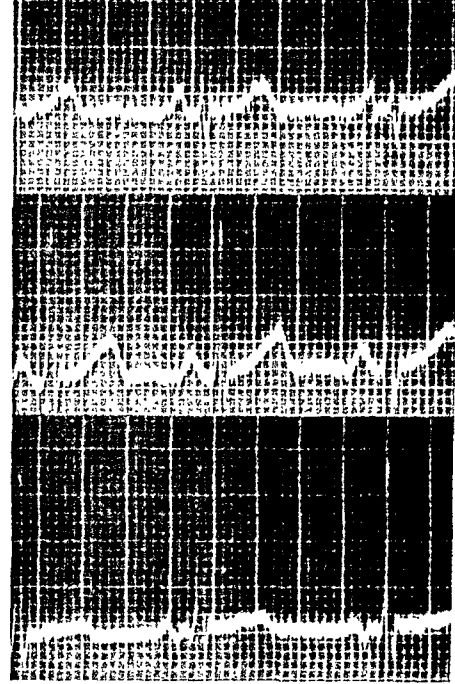


FIG. 1b

FIG. 1.—Case A. H. (584-297858), male, aged 16. Chronic rheumatic valvular disease, mitral stenosis and insufficiency: (a) roentgenogram March 10, 1931. Heart slightly increased to right and to left. Right auricular hypertrophy and enlargement of left ventricle. Prominence in region of left auricle and pulmonary conus. The lung markings are perhaps very slightly increased; (b) electrocardiogram March 11, 1931. Right ventricular preponderance; P waves large, indicating auricular enlargement; all T waves upright.

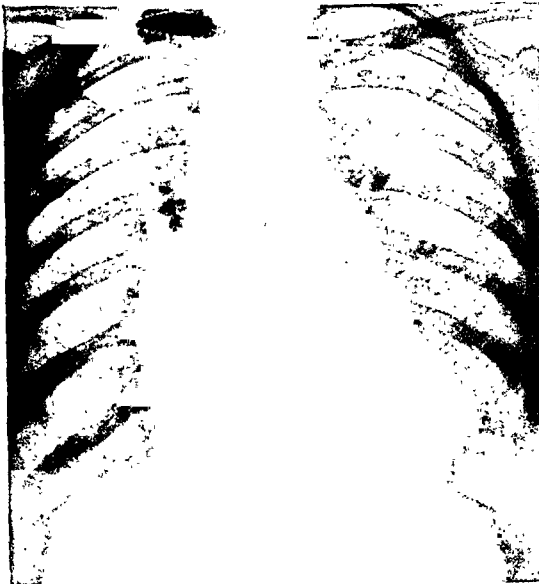


FIG. 2a

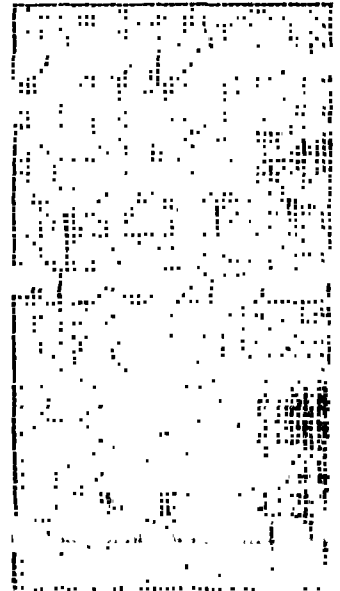


FIG. 2b

FIG. 2.—Case E. K. (71-286524), female, aged 24. Chronic rheumatic valvular disease, mitral stenosis: (a) roentgenogram May 24, 1929. Similar to Fig. 1 but more advanced. The heart is moderately enlarged, the right auricle is definitely hypertrophied, the bulge in the region of the pulmonary conus and left auricle more prominent. The lung markings are now moderately increased; (b) electrocardiogram May 25, 1929. Right ventricular preponderance, P waves large, inversion of T_I.

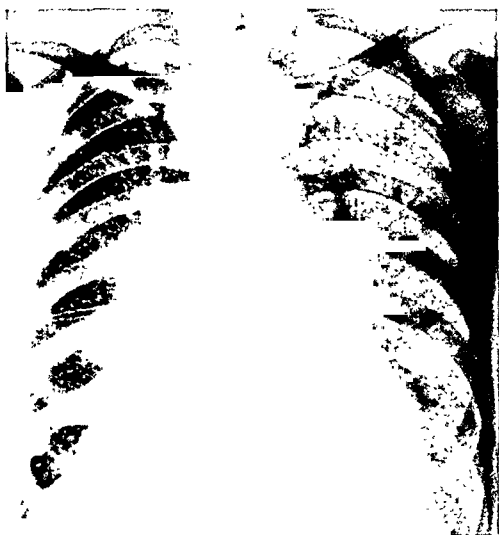


FIG. 3a

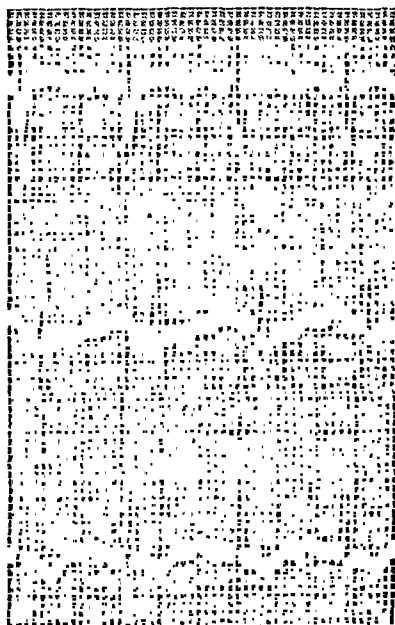


FIG. 3b

FIG. 3.—Case T. A. (9580-296363), male, aged 21. Chronic valvular disease, mitral stenosis and insufficiency, myocardial insufficiency, pulmonary infarct. Died January 1, 1931. (a) Roentgenogram December 4, 1930. Considerable enlargement of both ventricles, especially right. Huge bulge in region of pulmonary conus and marked accentuation of hilar and vascular shadows; (b) electrocardiogram December 4, 1930. Right ventricular preponderance; P waves large; semi-inversion of T_2 and inversion of T_3 .

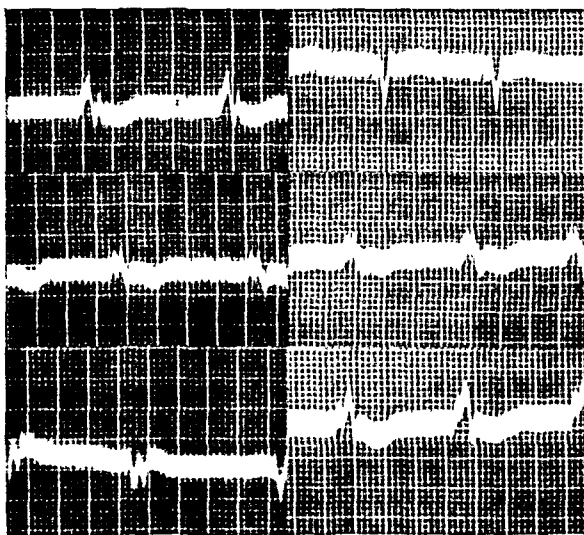


FIG. 4a

FIG. 4b

FIG. 4.—Case S. L. (198-271006), male, aged 56. General arteriosclerosis, coronary artery disease, auricular fibrillation, myocardial failure. Died February 16, 1928. (a) Electrocardiogram February 21, 1927. Left ventricular preponderance, inversion of T_1 and T_2 . (b) Electrocardiogram, same patient, February 2, 1928. Right ventricular preponderance, and now inversion of T_2 and T_3 .

ments the pulmonary artery was partially occluded, and T_3 negativity was produced in 1 case and a diminution of T_3 positivity in the other. From an investigation of patients with myocardial insufficiency Winternitz⁵ concluded that inversion of T_1 more than left ventricular preponderance was indicative of left ventricular hypertrophy and that T_3 inversion indicated right ventricular hypertrophy. He concluded that position and size of the heart chamber were the important agents in the production of inversion of the T-waves. He also cited the case of a man aged 59 suffering from myocardial degeneration and an enlarged heart who on maximal inspiration showed on the electrocardiogram right ventricular preponderance with T_{2-3} inversion, and on maximum expiration showed a left ventricular preponderance with a T_1 inversion. Since these electrocardiographic changes were not affected by vagal pressure or by the injection of atropin he concluded that change of position of the heart during respiration was the cause. He was of the opinion that a relation existed between left ventricular preponderance and T_1 inversion and right ventricular preponderance with T_3 or T_{2-3} inversions. Similarly, Pardee⁶ found an inversion of T_{2-3} in 25 per cent of the records which exhibited right ventricular preponderance, and inversion of T_1 in about the same percentage of records showing a left ventricular preponderance.

If one ventricle becomes unusually enlarged or hypertrophied, absolutely or relatively to the other ventricle, the T-wave has a tendency to be directed oppositely to the main deflection.

Although the relative or absolute position, shape and size of the heart chambers may determine the ventricular preponderance and the T-wave inversion, functional or toxic effects which influence the conduction pathways on one side of the heart alone or relatively one more than the other, will undoubtedly also produce such changes. In the series of 173 cases there were 11 patients who at one time showed a right ventricular preponderance and at another a left ventricular preponderance. Although these changes were temporary, when a right ventricular preponderance was present T_3 or T_{2-3} were inverted and when the left ventricular preponderance was present T_1 was inverted (Fig. 4). This electrocardiogram was from a man aged 56, on whom a diagnosis of arteriosclerosis of the coronary arteries with myocardial degeneration and general arteriosclerosis had been made. The first electrocardiogram revealed a left ventricular preponderance and T_{1-2} inversions, and the second a right ventricular preponderance and T_{2-3} inversions. The patient was fully digitalized on both occasions.

The great number of abnormal P-waves in the records showing right ventricular preponderance is evidence of auricular hypertrophy, particularly of the left auricle, since the predominant valvular lesion in all these cases is mitral stenosis.

The presence of the degenerative heart conditions, such as disease

of the coronary artery, myocardial degeneration and hypertension, among those that produce right ventricular preponderance was unexpected. A left ventricular preponderance is usually found in these conditions. In occlusions of the coronary artery, however, the axis deviation often changes (Fig. 4). In conditions such as arterial hypertension in which the left side of the heart is primarily involved, after a long interval of time the right side finally shares the burden and the right ventricle then enlarges.

Summary. The position, size and shape of one ventricle with respect to the other can be correlated with deviation of the electrical axis (ventricular preponderance) and inversion of the T-wave. Right ventricular preponderance with inversion of T_3 alone, or of both T_{2-3} , is characteristic of right ventricular enlargement. Left ventricular preponderance with inversion of T_1 is characteristic of left ventricular enlargement.

The inversion of T_3 or both T_{2-3} is commonly associated with right ventricular preponderance. Inversion of T_1 is commonly associated with left ventricular preponderance.

A more or less permanent T-wave inversion is not necessarily indicative of a pathologic process in the heart muscle.

As one ventricle definitely hypertrophies and enlarges, the T-wave has a tendency to become directed oppositely to the main deflection.

The groups of diseases associated with right ventricular preponderance are, in the first place, chronic valvular disease (57 per cent), with mitral stenosis alone or associated with other valvular lesions; in the second place, degenerative heart disease (21 per cent); and in the third place, non-cardiac disease, such as thyroid disease, bronchial asthma and emphysema; and finally, congenital heart disease and syphilis. Female individuals predominated by number in the patients with chronic valvular disease, and male individuals were in the majority in the degenerative heart disease group.

Right ventricular preponderance with inversion of T_{2-3} is associated with the most marked right ventricular enlargement, with the largest hearts, with the most marked enlargement of the pulmonary conus and the left auricle, with markedly increased lung markings and congestion in the lungs and with the highest mortality (33 per cent). Right ventricular preponderance with inversion of T_3 alone is associated with a less marked degree of these anatomic changes and a mortality of 15 per cent, and finally in right ventricular preponderance without any inversion of the T-wave at all, the least changes occur and the mortality is only 7 per cent.

Auricular fibrillation was present in 40 per cent of the patients showing right ventricular preponderance with both T_{2-3} inverted; 17 per cent when T_3 alone was inverted; and only 7 per cent with no T-wave inversion. In a patient under 50 years of age exhibiting right ventricular preponderance and auricular fibrillation, chronic disease with mitral stenosis is probably present, whether or not a

diastolic or other murmur is heard, and the etiology is probably a rheumatic disease.

In chronic valvular disease right ventricular preponderance appears to indicate the presence of mitral stenosis. In a patient who has chronic valvular disease and right ventricular preponderance the diagnosis of aortic insufficiency as the only valve lesion is practically eliminated.

In electrocardiograms of patients suffering from chronic valvular disease which show right ventricular preponderance, abnormal P-waves are very frequent, due to the presence of auricular hypertrophy resulting from mitral stenosis.

In the same patient there may occur a change from a left ventricular preponderance with T_1 inversion to a right ventricular preponderance with T_3 or T_{2-3} inversion, or a change from right ventricular preponderance with T_{2-3} inversion to a left ventricular preponderance with T_1 inversion.

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THE EFFECT OF THE HEART'S POSITION ON THE ELECTRO-CARDIOGRAPHIC APPEARANCE OF BUNDLE-BRANCH BLOCK IN MAN.*

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(From the Heart Station of the Michael Reese Hospital.)

KATZ and Ackerman¹ studied the effect on the electrocardiogram of changing the position of the heart in experimentally produced bundle-branch block. They found that a change in the heart's position caused a noticeable shift of the electrical axis. At times

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there occurred a complete reversal of the directions of the $Q-R-S$ deflections of Leads I and III. This indicated that in bundle-branch block the position of the heart, as well as the site of the block determines the direction of the $Q-R-S$ deflections.

The present investigation was made to discover if such changes could be demonstrated in man. In 6 individuals with so-called right bundle-branch block (older nomenclature) electrocardiograms were taken in various positions of the body and in different phases of respiration. Tracings were taken with the subject (a) lying on the back, (b) on the left side, (c) on the right side, (d) on the abdomen, (e) sitting up, (f) in deep inspiration and (g) in deep expiration.

Some degree of shift in the electrical axis appeared with change in position of the heart in every case. Twice, marked change in the electrical axis appeared. In these 2 cases, as shown in Figs. 1 and 2, a so-called right bundle-branch block (older terminology) became an indeterminate type. The change in the heart's position caused the $Q-R-S$ deflection in Lead III to change from negative to positive, while in Lead I the $Q-R-S$ deflection became smaller. The changes that occurred were not as marked as in the animal experiments since the degree of movement of the heart was more limited under the conditions of this investigation.

These results bear out the contention of Katz² that the direction of the $Q-R-S$ deflection in the electrocardiogram in bundle-branch block is determined by the position of the heart as well as by the site of the block.

Krumbhaar,³ Luten and Grove,⁴ and Hyman and Parsonnet⁵ have taken serial electrocardiograms which show the gradual development of bundle-branch block. We have seen similar records. Cases of right bundle-branch block (older terminology) were preceded by left axis deviation and a case of "left" bundle-branch block⁵ was preceded by right axis deviation. This fact would support the original contention that the position of the heart—and this would include hypertrophy and dilatation—plays a rôle in the electrocardiographic configuration of bundle-branch block. This interpretation may serve to explain the apparent discrepancies between clinical and necropsy findings in certain cases of bundle-branch block.

Summary and Conclusion. 1. In 2 cases of so-called right bundle-branch block (older nomenclature), shift in the position of the heart changed the electrocardiogram to the indeterminate type of bundle-branch block.

2. The position of the heart as well as the site of the blocked bundle-branch determine the direction of the $Q-R-S$ in the electrocardiogram of bundle-branch block. This may be the explanation of certain apparent contradictions in the findings of previous students of bundle-branch block.

3. It is suggested that electrocardiograms heretofore interpreted as left and right bundle-branch block be reported simply as intra-

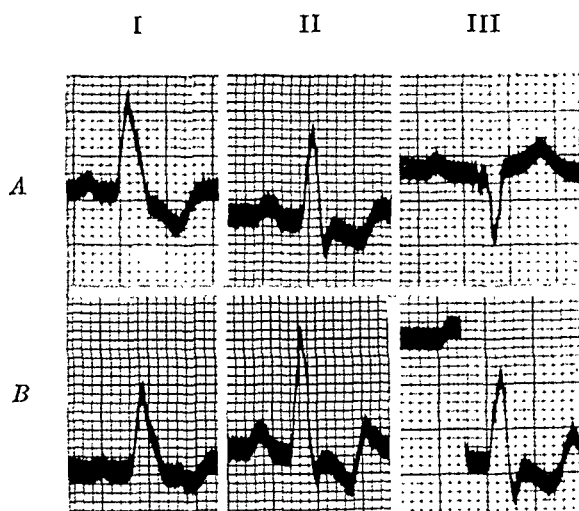


FIG. 1.—Case 2. *A*, Electrocardiogram taken with patient on back; *B*, lying on left side.

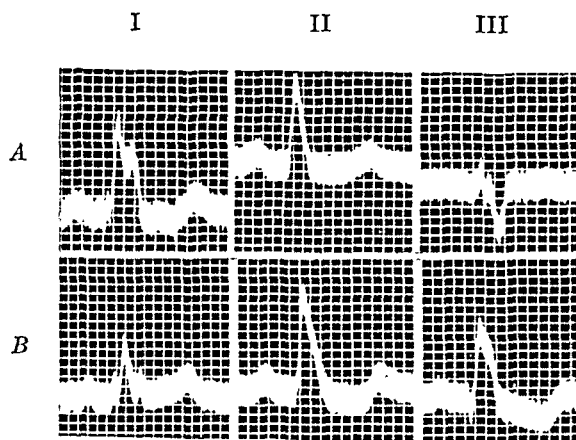


FIG. 2.—Case 6. *A*, Electrocardiogram taken with patient sitting; *B*, lying on left side.

ventricular block of "bundle-branch block configuration" and that no attempt be made to locate the blocked bundle-branch from the electrocardiographic appearance alone.

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3. Krumbhaar, E. B.: Transient Heart Block: Electrocardiographic Studies, *Arch. Int. Med.*, 1917, 19, 750.
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REVIEWS.

INTERNAL MEDICINE. ITS THEORY AND PRACTICE. By various contributors. Edited by JOHN H. MUSSER, B.S., M.D., F.A.C.P., Professor of Medicine in the Tulane University of Louisiana School of Medicine; Senior Visiting Physician to the Charity Hospital, New Orleans. Pp. 1316; 37 illustrations. Philadelphia: Lea & Febiger, 1932. Price, \$10.00.

To quote from the preface: "The ever increasing complexities of internal medicine and the steadily mounting mass of facts that pertain to disease make it an impossibility for any one man to write with authority on such a large subject." This is the second one-volume textbook written by numerous contributors that has appeared in recent years. The advantage of such a book from the standpoint of factual excellence in all its sections is obvious. The editor of such a volume is, however, confronted with the necessity of avoiding certain pitfalls and difficulties. The larger the number of contributors, the greater is the task of proper coördination, of proper emphasis as determined by space assigned to various subjects, of avoidance of duplication. Again, not every medical author combines with his knowledge of the subject the facile vivid expression of an Osler, a Strümpell or a Dieulafoy. The editor is to be congratulated on his happy solution of these problems. The 27 writers who have contributed to this volume all hold professorial appointments in medical schools and as teachers are experienced in imparting their information to students. Worthy of comment is the inclusion of an excellent chapter on mental disorders. This volume will take its place as a standard text in American medical literature. R. K.

VARICOSE VEINS AND HEMORRHOIDS. By V. MEISEN, M.D., former Chief Surgeon to the Policlinic, Sundby Hospital, Copenhagen. With a Preface by AUG. KROGH, PH.D. Pp. 149; 25 illustrations, 8 colored plates. Copenhagen: Levin & Munksgaard, 1932; London: Oxford University Press, 1932.

THIS is an attempt to cover the entire field of injection of sclerosing agents to benefit varicose veins, hemorrhoids, varicocele, hydrocele and venous angioma.

In the section on varicose veins of the leg, the chapters on the anatomy and physiology are well done. Much space has been properly given to the consideration of deep vein phlebitis and postphlebitis sequelæ and complications. The various contraindications to both the injection and operative treatments are scantily treated, while treatment following deep vein phlebitis is somewhat rashly advocated. The technique is clearly given and follows closely the accepted methods. One is disappointed that more has not been given on recurrences, canalization of the thrombosis, newly formed veins and those cases that resist all sclerosing agents—questions that are now particularly engaging the thought of surgeons.

The injection of varicocele will meet with little enthusiasm and few

surgeons have anxiously awaited a new substance with which to inject hydrocele.

In the section devoted to hemorrhoids the general similarity between varicose veins of the leg and of the rectum is overemphasized, overlooking the important differences in the anatomy of the veins and the course of the circulating blood in varicose veins of the leg and of the rectum. For instance, in varicose veins of the leg it is pointed out that the direction of flow of the blood is downward to the deep veins through the communicating ones which are smaller and, therefore, the possibility of an embolus passing into the general venous circulation remote. This is not the arrangement in the rectum, however, and, the flow being from the smaller to increasingly larger veins, the greater chance of embolism is apparent.

Infection of most hemorrhoids was pointed out, but though fatal cases have been reported, the unsound practice of injecting into an infected area a highly irritating solution devitalizing to the tissues is recommended.

In referring to the surgical treatment of hemorrhoids, the author has denounced the clamp and cautery method because of the resulting stenosis and ectropion of the mucosa. However, stenosis of the rectum should not occur if the clamp is applied in the direction of the long axis of the rectum rather than on the circumference. Recurrences of hemorrhoids after the injection treatment has not been discussed.

In the hands of the general practitioner and inexperienced surgeon the book would give the unsupported and unwarranted view that the injection treatment of varicose veins of the leg and hemorrhoids had satisfactorily supplanted the surgical treatment of both these conditions and that shortly it might be equally well applied in the treatment of varicocele, venous angioma and varicocele. S. W.

Un Pericolo Sociale: Le Brucellosi. By PROF. A. ALESSANDRINI and M. PACELLI, M.D., with a Preface by PROF. A. ILVENTO, Vice-Director General of the Public Health Service. Pp. 184; 10 illustrations. Rome: Edizioni "Annali d'igiene," 1932.

EXCEPT for their failure to refer to Keefer's first report of proved human infection by the organism of contagious abortion of cattle, and the early work of American clinicians in delineating this phase of the disease, the authors have given a detailed presentation of the problem of Brucella infections, a problem which by the Section on Hygiene, League of Nations, was designated as "one of the most important world problems of public health." There are chapters dealing with the prevalence of brucellosis in man and animals in the various countries; the bacteriology of Brucella; the sources of contagion; prophylactic measures against brucellosis in the commonly affected domestic animals and in man; milk in relation to undulant fever. Complete from the Italian point of view, this monograph is, as far as the Reviewer knows, the most comprehensive in any language on the public health aspects of this subject. R. K.

SANE SEX LIFE AND SANE SEX LIVING. By H. W. LONG, M.D. With a Special Introduction by DR. W. F. ROBIE. Pp. 151. New York: Eugenics Publishing Company, Inc., 1922. Price, \$2.

A book which aims to "improve health, prolong life and promote virtue" by giving in non-technical language details of sexual life. Necessarily sold only to medical men, it is written for the laymen and much space

given to exhortation. Restricted to the right sort of reader, it doubtless would have its uses, though occasional strange bits of physiology are included. How to prevent the book from falling into the wrong hands is a problem that apparently does not concern author or introducer.

E. K.

FILTERABLE VIRUS DISEASES IN MAN. By JOSEPH FINE, M.D., B.Sc., D.P.H. (GLAS.), D.T.M. (LIVERP.), Assistant to the Professor of Public Health, Edinburgh University; formerly Research Assistant, Sir Alfred L. Jones Laboratory (Liverpool School of Tropical Medicine), Freetown, Sierra Leone; late Assistant Pathologist, Ancoats Hospital, Manchester. Pp. 144. Baltimore: William Wood & Co., 1932. Price, \$2.25.

THE status of filterable virus diseases today is much the same as was the status of bacteriology about forty years ago: Our knowledge is so rapidly expanding that only the specialist can hope to keep even reasonably well informed. It is, therefore, desirable to have at not too infrequent intervals summaries and critical reviews of the important subject. This appears to be the object of the little book by Fine. It is well written, and it contains in compact form the essential parts of virus diseases in man. Moreover, it makes available in a single volume the recent advances in our knowledge. The references given at the end of each chapter, while not an exhaustive list of the literature, are a good guide for those who wish to become better acquainted with a fascinating field of pathology and clinical medicine.

The author's attempt to classify and systematize the virus diseases of man is helpful to the non-specialist. We wish to recommend this very readable book to all who would gain at least some acquaintance with a rapidly progressing part of medicine.

B. L.

FUNCTIONAL DISORDERS OF THE GASTRO-INTESTINAL TRACT. By WILLIAM GERRY MORGAN, M.D., F.A.C.P., Professor of Gastroenterology, Georgetown University Medical School, etc. Pp. 259; 32 illustrations. Philadelphia: J. B. Lippincott Company, 1931. Price, \$5.00.

ONE of the volumes of the Everyday Practice Series, under the editorship of Dr. Harlow Brooks, this book deals with the diagnosis and treatment of the various abnormalities of function of the digestive tract. The viewpoint is conventional and the presentation is conservative. There are numerous illustrative case reports.

R. K.

THE ACTION OF THE LIVING CELL: EXPERIMENTAL RESEARCHES IN BIOLOGY. By FENTON B. TURCK. Pp. 308; 17 illustrations. New York: The Macmillan Company, 1933. Price, \$3.50.

SOME years ago the author, who died last November, isolated a substance which he named *cytost*. This he regarded as a cellular toxin which, being suddenly liberated in large quantities by injured tissues, caused shock and death. Not only did he recognize that the composition of *cytost* "is a biochemical problem which still awaits solution," but unfortunately so many of his views remained highly speculative theories and of his observations remained insufficiently controlled that they have not carried great weight

with students of the subject. Like Finley's views on the relation of the mosquito to yellow fever, or many of Sajous' theories of endocrine action, they remain as perhaps brilliant flashes of intellect which very rarely are of any value in substantially advancing biological science. The material accumulated in the book under the review in the opinion of the Reviewer only partly obviates this criticism.

E. K.

EL ASMA Y OTRAS ENFERMEDADES ALÉRGICAS. By DR. CARLOS JIMÉNEZ DIAZ. Pp. 945; 88 illustrations, some colored. Madrid: Editorial España, 1932. Price, 60 pesetas.

AN unusually complete and well-balanced presentation of the subject and by all odds the best European text on allergic disorders that has come to our attention. The first third of the book deals with the theory, mechanism and etiology of allergy. Then follow 60 pages on the general symptomatology and diagnosis of allergic states. The rest of the volume deals with the various clinical manifestations of allergy, half the space being devoted to the allergic diseases of the respiratory tract, and the other half to allergic skin disorders, angioneurotic edema, migraine, and allergy in the digestive tract and elsewhere. It is in the field of digestive allergy that the author has made original contributions. Minor criticism: the lack of an index. There is a very extensive bibliography, thoroughly representative of the medical literature of the world. The book should prove most useful to all physicians who read Spanish.

R. K.

CLINICAL INTERPRETATION OF LABORATORY REPORTS. By ALBERT S. WELCH, A.B., M.D., Clinical Instructor in Medicine in the University of Kansas School of Medicine in Kansas City, Kansas, etc. Pp. 366; 16 illustrations, 1 in color. Philadelphia: P. Blakiston's Son & Co., Inc., 1932. Price, \$4.00.

THE ever increasing use of laboratory procedures in the diagnosis of disease confronts the practitioner with the growing necessity of interpreting and evaluating the reports he receives from the laboratory. He will find a conservative and accurate guide in this book, the author of which is both clinician and pathologist.

R. K.

THE NERVOUS CHILD AT SCHOOL. By HECTOR CHARLES CAMERON, M.A., M.D. (CANTAB.), F.R.C.P. (LOND.), Physician in Charge of Children's Department, Guy's Hospital. Pp. 160. New York: Oxford University Press, 1933. Price, \$1.50.

THE theme is largely fatigue, expressing itself chiefly as vomiting and bilious attacks, abdominal pains and sensations, persistent rise of temperature, fainting and cardiovascular disorders, attacks of unconsciousness and convulsions, and disorders of sleep. Continuing, disorders of conduct are considered, as persistent lying, stealing, playing truant and masturbation. Considerable assurance is shown and exception may be taken to this statement: "But there is no such thing as a child of high intelligence who, in point of morals only, is imbecile."

A criminal of high intellectual endowment, robust and a writer of note, began to read at three and a half years and entered upon a life of crime

at nine. He was in a reformatory, a county jail and a penitentiary. Once, when arrested, there were 29 charges against him. He said he was always kindly treated as a child, had attended a private school, a primary school and a college. At 21 he inherited \$34,000, spent it in 3 years and later in life received help from many prominent persons, yet he showed no self-reproach. He stated to Reviewer: "There is a born criminal and I am one." When last seen, he was 48 years old and was debating whether to return to crime or accept matrimony from a woman of some means and culture.

N. Y.

LIGHT THERAPY. By FRANK HAMMOND KRUSEN, M.D., Director of the Department of Physical Medicine, Temple University School of Medicine, Philadelphia. Foreword by JOHN A. KOLMER, M.D., Dr.P.H., D.Sc., LL.D., Professor of Medicine, Temple University School of Medicine. Pp. 196; 33 illustrations. New York: Paul B. Hoeber, Inc., 1933. Price, \$3.50.

A WELL written and illustrated monograph designed for the general practitioner. Light as a therapeutic agent and its manner of use are written of with clarity. What is not known concerning the subject is outlined; its therapeutic limitations are stressed; its proven values are detailed. The entire subject is treated authoritatively and without bias. The book is worth while.

G. W.

THE BIOCHEMISTRY OF MEDICINE. By A. T. CAMERON, M.A., D.Sc., F.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba; Biochemist, Winnipeg General Hospital; and C. R. GILMOUR, M.D., C.M., F.R.C.P. (C.), Professor of Medicine and Clinical Medicine, University of Manitoba; Physician, Winnipeg General Hospital. Pp. 506; 31 illustrations. Baltimore: William Wood & Co., 1933. Price, \$7.25 (temporary price, \$5.50).

THIS volume is a useful addition to that field of publication—the application of biochemistry to clinical medicine—so brilliantly inaugurated by the *Quantitative Clinical Chemistry* of Peters and Van Slyke. The authors, realizing the limitations of their shorter work, constantly refer to the American treatise, which seems destined for many years to serve as a model. The Reviewer agrees with the authors that *The Biochemistry of Medicine* may have a distinct field of usefulness for the less advanced "student of medicine receiving clinical instruction . . . and for the physician who received no special instruction in the medical applications of biochemistry."

The book deals adequately with such topics as glycosuria, sugar tolerance curves, the biochemistry of diabetes, anomalies of metabolism, anemias, edema, and renal, gastric and liver functional tests. Each chapter is followed by a moderately extensive bibliography and short summary.

A short work must of necessity suffer somewhat from arbitrary discussions, and a first edition often suffers from errors of omission as well as commission. The following is, therefore, offered in the spirit of looking forward to an improved second edition: (1) In the discussion of adrenalin hyperglycemia, no account is taken of the phenomenon of preferential burning of fat. (2) *In vivo*, during exercise, the respiratory quotient is but rarely 1, as the authors assume. Furthermore, it is erroneous to state "during muscular exercise the chief oxidation in the organism is that of lactic acid of muscle." (3) It would appear in a book of this type far less

important to discuss heptosuria, which has never been proved adequately, than to discuss such topics as the influence of type of food fat upon type of fat produced in the body—a problem of some medical interest. (4) In the discussion of synthalin, the idea of its possible value is conveyed, whereas many publications stress rather the liver damage that this drug causes. (5) The data in the chapter on the metabolism of water might well, at present, be presented in osmolar terms. (6) The section on edema is relatively poor. Too much space is devoted to the theories of Fischer, none at all to the recent important work upon the relationship of serum proteins to edema. (7) "Conant and Scott have furnished proof that methemoglobin has only one-half of the removable oxygen of oxyhemoglobin. It (oxygen) is held more firmly than that in oxyhemoglobin, so that hemoglobin cannot function as an oxidation carrier." The authors have misquoted the work of Conant and Scott, and apparently have not realized that oxygen *per se* is not concerned with the oxidation of hemoglobin to methemoglobin.

In spite of these various suggestions, the Reviewer favorably recommends this short treatise to the intern and practitioner of medicine. D. D.

NOSOKOMEION. QUARTERLY HOSPITAL REVIEW. No. 2, APRIL, 1933. Containing the Proceedings of the Third Hospital Congress. Pp. 441. Stuttgart: W. Kohlhammer.

This number of the official organ of the International Hospital Association contains the reports and proposals of the Third International Hospital Congress recently held at Knocke Sur Mer, Belgium. For the convenience of all of its members it is printed in five languages. The work of its Study Committee, dealing as it does with the construction, equipment, administration, services and finances of hospitals throughout the civilized world, has as its far-reaching effect not only the dissemination of information concerning hospital practices but also a strong tendency toward standardization of procedures and techniques. Not only is this issue of the greatest practical value to those interested in hospitals because it summarizes world beliefs and practices, but it serves also to discourage the setting up of any climatic, racial or language boundaries in so far as they effect the principles and practice of caring for the sick. J. D.

SURGICAL ANATOMY. By C. LATIMER CALLANDER, A.B., M.D., F.A.C.S., Assistant Clinical Professor of Surgery and Topographic Anatomy, University of California Medical School; Associate Visiting Surgeon to the San Francisco Hospital. With a Foreword by DEAN LEWIS, M.D., Sc.D., LL.D., F.A.C.S. Pp. 1115; 1280 illustrations, some in colors. Philadelphia: W. B. Saunders Company, 1933. Price, \$12.50.

This volume has, on the whole, been beautifully prepared and printed and fills a real need in the field of surgical anatomy. The many chapters cover the entire field of surgical anatomy. The author states that, with his father, "Recognizing accurate anatomic knowledge as the basis of surgical technique, we planned to present anatomic facts in terms of their clinical approaches, the paths of extension of pathologic processes, and the common operations. We worked together assembling and organizing material until three years ago when I was left to finish alone.

"This text is not a systematic treatise; it is intended to be explanatory

and utilitarian rather than encyclopedic. To avoid repetition of material, cross-referencing is used throughout. Most of the illustrations are original drawings of dissected material. If any of them are derived from sources not credited, the oversight is unintentional."

The illustrations are good; some, of course, would have been enhanced by the use of color. The anatomic data are well presented. Surgical technique is discussed briefly and the various operative steps are often illustrated. As Dr. Lewis says in the Foreword, the "book is printed with the definite idea of indicating the paths of surgical approach to the pathologic process which is to be removed or corrected."

While certain subjects are so familiar to the experienced surgeon that prolonged discussion may seem unnecessary, for the student and young surgeon these may be of first importance. From this point of view, the author has given too little space to the surgical anatomy of the appendix. There is, of course, the ever-present danger of attempting to cover so much ground that the book really becomes an abridged textbook of anatomy with added surgical implications. By way of further criticism from the student and clinical standpoint, it is better to discuss the anatomy from the viewpoint of the surgeon rather than the anatomist. The illustrations often have so many leads (Fig. 316 has 41) that the result is one of confusion rather than clarity.

This book should be well received and the author is to be congratulated on the work he has done.

I. R.

ROENTGENOGRAPHIC STUDIES OF THE URINARY SYSTEM. By WILLIAM E. LOWER, M.D., F.A.C.S., Chief of Department of Urology, Cleveland Clinic; former Associate Professor of Genito-Urinary Surgery, Western Reserve University; Surgeon to Cleveland Clinic Hospital; and BERNARD H. NICHOLS, M.D., F.A.C.R., Chief of Department of Roentgenology, Cleveland Clinic. Pp. 812; 812 illustrations. St. Louis: The C. V. Mosby Company, 1933. Price, \$16.

THIS is but the third book to appear in this country presenting the interpretative value of roentgenology in urology. It differs markedly from its predecessors in its format. Recognizing that the urologist has much to learn concerning the interpretation of roentgenograms, and that the roentgenologist has infinite need to become familiar with the depiction and recognition of urologic pathology and its surgical indications, this book devotes but 70 pages to technical methods and pathologic conditions, with a brief and interesting chapter on other lesions of the upper right quadrant; to be followed by 733 pages depicting the roentgenographic findings in 443 case studies. Each case is presented with a brief history, clinical findings, cystoscopic report, roentgenographic interpretation and surgical diagnosis. It is an atlas presenting the most complete exposition of the subject in all its phases. The plates are exquisitely reproduced and their interpretation aided by miniature-graphs that are unique and intrinsically valuable.

A. R.

INTRACRANIAL TUMORS. By PERCIVAL BAILEY, Professor of Surgery, University of Chicago. Pp. 475; 157 illustrations. Springfield, Ill.: Charles C Thomas, 1933. Price, \$6.00.

In the Preface we read that "the time is past when discussions of intracranial tumors as a whole can longer be profitable. It is true that such tumors, if allowed to develop long enough, have this in common that they

give rise to intracranial hypertension. So may abdominal tumors cause enlargement of the belly, yet who would think of discussing fibroma of the uterus, carcinoma of the liver and ovarian cyst as though they were similar lesions?"

After a brief but excellent discussion of the problems of tumors in general, the cranial tumors in particular are discussed, their origins explained and the varieties classified. Following this comes an excellent description, well illustrated, of the anatomy and physiology of the parts concerned. The individual tumors are then taken up. For each there is a preliminary description of the appearance, gross and microscopic, of the seat of occurrence, the anatomical injuries effected, the physiologic disturbances that inevitably follow; and then a series of case studies emphasizing these points and bringing out so far as possible the diagnostic differential points of the tumor under consideration.

The text is excellent, entertaining and profitable and is illustrated by drawings that seem adequate for their purpose, though, as compared with the photomicrographs that might have been introduced but for the author's objection to glazed paper, they leave much to be desired.

Surgical treatment, regarded as of interest to the specialist only, is touched upon very sketchily, the purpose of the work being to enable the reader to understand the tumors, not operate upon them. J. McF.

PRÉCIS D'ANATOMIE PATHOLOGIQUE. In two volumes. By G. ROUSSY, R. LEROUX and CH. OBERLING. Pp. 1344; 582 illustrations. Paris: Masson et Cie, 1933.

ALL pathologists should know of this work of three of the best-known French pathologists. Americans have for a generation or more received their chief inspiration from German investigators and have, in consequence, become most familiar with their language and output. But one of the results of the World War was to bring about an interest in French literature and science, showing that another great people had been and is actively investigating and producing. This book is a striking example of their good work. In two volumes, conveniently small, with superb illustrations, mostly drawings, and a text brief and to the point, the subject is presented in every modern detail. J. McF.

HISTORY OF UROLOGY. In Two Volumes. Prepared under the auspices of the American Urological Association. Editorial Committee: EDGAR G. BALLENGER, WILLIAM A. FRONTZ, HOMER G. HAMER, BRANSFORD LEWIS, Chairman. Pp. 746; 49 illustrations. Baltimore: The Williams & Wilkins Company, 1933. Price, \$8, set.

THESE two authoritative and well-documented volumes make it difficult to realize that urology as a specialty had its start in the seventies and that even by 1902, when the American Urological Association was formed, specialists in this field were but few. The present work gives a comprehensive historical review of the development of urology, chiefly in America, with especial emphasis on the achievements of the Association which sponsored the preparation of the work. The plan adopted is to devote a chapter apiece to the Association, to New York, Philadelphia, Boston, Baltimore, Chicago, the Middle West and the West Coast, to be followed by 22 further chapters on various important urologic topics, all by different and well-known authors. In these chapters the subject has been followed

since ancient times, though necessarily the most space is devoted to modern developments. Especially interesting to the general reader is Dr. Caulk's 35-page chapter on Outstanding Contributions to Urology, which, pardonably enough, emphasizes the American contributions and again brings out the tremendous development of the subject during the present century. The work is well turned out and reasonably free from errors, though meagerly illustrated. Its chief defect—and a serious one—is the absence of an index, thus offsetting much of the value of its documentation.

E. K.

BOOKS RECEIVED.

NEW BOOKS.

Life in the Making. By DR. ALAN FRANK GUTTMACHER, Associate in Obstetrics, Johns Hopkins University; with the assistance of ELLERY RAND. Pp. 297; 8 illustrations. New York: The Viking Press, 1933. Price, \$2.75.

The Surgical Clinics of North America, Vol. 13, No. 4 (Mayo Clinic Number, August, 1933). Pp. 215; 65 illustrations. Philadelphia: W. B. Saunders Company, 1933.

International Clinics, Vol. 3, Forty-third Series, September, 1933. By Various Contributors. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore. Pp. 316; illustrated. Philadelphia: J. B. Lippincott Company, 1933.

Paralysis in Children. By R. G. GORDON, M.D., D.Sc., F.R.C.P. (EDIN.), Physician, Bath and Wessex Orthopædic Hospital; Physician, Royal United Hospital, Bath, etc.; and M. FORRESTER BROWN, M.D., M.S. (LOND.), Surgeon, Bath and Wessex Orthopædic Hospital; Surgeon to County Orthopædic Clinics, Wiltshire, Somerset and Dorset. Pp. 328; 116 illustrations. New York: Oxford University Press, 1933. Price, \$4.50.

The Diagnosis and Treatment of Diabetes. By W. WILSON INGRAM, M.C., M.D. (ABER.), Honorary Physician and Physician-in-Charge of the Clinic for Diabetes Mellitus, Royal North Shore Hospital, Sydney, etc.; and G. V. RUDD, M.Sc. (MELB.), Research Biochemist, Institute of Medical Research, Royal North Shore Hospital, Sydney. With a Preface by C. G. LAMBIE, M.C., M.D., F.R.C.P., F.R.S.E., Bosch Professor of Medicine, University of Sydney. Pp. 88; illustrated. Australia: Angus & Robertson, Ltd., 1933.

Clinical Science Incorporating Heart, Vol. I, No. 1. Edited by THOMAS LEWIS, M.D., F.R.S., aided in the selection of papers by T. R. ELLIOTT, M.D., F.R.S., R. T. GRANT, M.D., P. P. LAIDLAW, F.R.S., EDWARD MELLANBY, M.D., F.R.S., WILFRED TROTTER, M.S., F.R.S., and E. B. VERNEY, F.R.C.P. Pp. 158; illustrated. London: Shaw & Sons, Ltd., 1933. Price, 37/6.

Un Pericolo Sociale: Le Brucellosi. By PROF. A. ALESSANDRINI and M. PACELLI, M.D., with a preface by PROF. A. ILVENTO, Vice-Director General of the Public Health Service. Pp. 184; 10 illustrations. Rome: Edizioni "Annali d'igiene," 1932.

(For Review see page 725.)

PROGRESS OF MEDICAL SCIENCE --- MEDICINE

UNDER THE CHARGE OF

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The Effect of Restriction of Protein Intake on the Serum Protein Concentration of the Rat.—A great deal of interest has been occasioned by the frequently confirmed observation that in certain types of Bright's disease and in certain conditions of undernourishment there is a well-marked hypoproteinemia. In the case of Bright's disease this is attributed to the loss of protein as albumin in the urine and in the states of undernutrition to a protein want from dietary inhibitions or insufficiency. At times it is conceded that both factors may play a part in the production of edema. BLOOMFIELD (*J. Exp. Med.*, 1933, 57, 705) deems it advisable to analyze critically the mass of evidence for what he terms the loss and lack theory and to point out that there may be some other causative factors which play a part in this condition. He very fairly presents the arguments in favor of this protein loss and lack conception of the cause of edema. He then considers the published reports of those who are qualified and discusses their experiments. For example, he states that in Leiter's experiments the withdrawal of plasma was excessive and is not likely to be paralleled in man. In Whipple's experiments the dogs built up their protein to normal level even after fasting for a period of 2 weeks. Protein loss, he concedes, may lower blood proteins, but it must be excessive. In case of the observations of Peters and others he feels that it is quite possible that there was an actual disturbance of the protein-building mechanism to explain the hypoproteinemia. In conjunction with Bright's disease, the protein urinary loss should bear some direct relationship to blood proteins. It should be expected that these should be termed normal or a higher level if large quantities of protein were given by mouth. Even in extremely heavy proteinuria, plasma proteins in some instances were moderately low, whereas others with less extreme proteinuria had under 4 grams per cent. Even more striking are the experiments of Peters and Bulger, who fed high-protein diets to nephritics with low blood proteins. Irrespective of the diet and the loss or storing of nitrogen, blood proteins remained at a fairly constant level, indicating that the low blood protein was not related to nitrogen metabolism of the body as a whole, but rather to some special failure of the blood protein

mechanism, possibly exaggerated by the proteinuria. Again, it is possible to find low blood proteins in well-nourished individuals who have not suffered from a protein dietary deficiency. In order further to substantiate his ideas, a series of experiments were carried out by Bloomfield with mature rats. They were given an experimental diet without carrots but adequate in calories, salts and vitamins and with a minimum of protein. The serum proteins of these animals were examined *en masse* after prolonged dietary observation, during which time the animals remained entirely well. In the first initial period there was a fall in the concentration of serum proteins of approximately 10 per cent at the expense of serum albumin. Upon a return to a diet with adequate protein there was an equally prompt restoration to the initial serum protein level. These fluctuations are very rapid and so slight it is presumed they are physiologic rather than pathologic. There was no further drop of significance during a period of 20 weeks, corresponding to a period of 10 years of human life. In the killed rats who were sacrificed on the 147th day the albumin-globulin ratio was within normal range. In a group of rats, at the end of the 20-week period, placed on a control diet with casein 16 per cent, the serum protein rose very promptly. On a starvation diet there was an initial drop but no further significant changes. The results of these experiments did not accord with those of many others. Bloomfield suggests that the subject needs further study and the exact nature of the mechanism requires special analysis. There may be other possible etiologic factors, such as vitamin deficiency, excess of certain foods, such as carrots, insufficient caloric intake, and infection, to be considered.

SURGERY

UNDER THE CHARGE OF

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Larvæ Therapy.—Numerous references are to be found in the literature of ancient, medieval and modern medicine concerning the beneficial results from the introduction of maggots in various types of wounds. Flies have deposited their eggs and larvæ have developed in poorly cared for wounds of men and animals since the dawn of history, and it is not surprising that the effects of fly larvæ on wounds have been frequently described. It is surprising, however, that the descriptions of PARÉ (*Les Œuvres d'Ambroise Paré*, ed 2, p. 1576; ed. 11, A. Lyon; Pierre Rigaud, 1652; translation from the Latin by Theodore Johnson, London, Clark, vol. 10, p. 249; vol. 11, pp. 277, 1678; *Selections from the Works of Ambroise Paré*, by Singer, 1924, p. 218) and LARREY (*Observations on Wounds, and Their Complications by Erysipelas, Gangrene and Tetanus, etc.*, translated from the French by E. F.

Rivinus, Philadelphia, Key, Mielke and Biddle, 1832, p. 34; *Clinique Chirurgicale*, Paris, 1929, pp. 51, 52) and the occasional later references to the effect of maggots were largely ignored until BAER (*Proc. Inter-State Post-Grad. Med. Assn. of North America*, Detroit, 1929, p. 370) introduced maggot therapy as a major part of the treatment of osteomyelitis in 1929.

GOLDSTEIN (*J. Bone and Joint Surg.*, 1931, 13, 476) has reviewed the literature of maggot therapy previous to Baer's publication. While an occasional observer had recognized that a wound which had become contaminated with maggots was possibly benefited by their presence, most clinicians have felt that a wound containing maggots was detrimental as well as repulsive to the patient and indicated poor wound care.

BAER'S (*J. Bone and Joint Surg.*, 1931, 13, 438) results indicated in a striking manner that larvæ of the blow-fly aided in the healing of cases of osteomyelitis. The lesions which he reported healed more rapidly than if surgery alone had been resorted to, appeared cleaner and the granulation tissue looked healthier. Baer did not account entirely for the beneficial results of this type of therapy. He felt, however, that the maggots ate the necrotic tissue and caused changes in the hydrogen-ion concentration of the fluid in the wound which was beneficial to wound healing. His description of the action of the maggots intimated that the maggots have an instinct for cleaning wounds and that they ate ravenously to remove all necrotic material and to loosen sequestra.

MARTIN and HEEKS (*Ann. Surg.*, 1932, 96, 930) point out that on the basis of the entomological studies of FABRE (*Souvenirs Entomologiques [Dixieme Serie] La Mouche Bleue de la Viande-Le Ver*, p. 259; Laponte, p. 241) maggots are not true scavengers in that they cannot subsist on solid food but must live on a liquid diet. In addition, these authors felt that Baer's results did not indicate that larval therapy has any advantages over the Orr method of treatment of osteomyelitis.

Since Baer's original paper many reports have appeared which substantiate Baer's contention that maggot therapy is an efficacious method for the treatment of osteomyelitis. The manner by which these results are brought about is, however, not so well understood. Naturally the most plausible explanation is that the maggots act as scavengers, eating bacteria and tissues that have become necrotic and soft. WEIL, SIMON and SWEADNER (*Am. J. Surg.*, 1933, 19, 36) reported that in addition to a scavenger effect the larvæ produce an excretory proteolytic substance which hastens liquefaction. LIVINGSTON and PRINCE (*J. Am. Med. Assn.*, 1932, 98, 1143) state that the effects are due to an active principle which they are able to extract from the dead bodies of maggots. These authors treated 100 cases of primary osteomyelitis, infected wounds, and infected compound fractures with maggot extract and polyvalent vaccines, and obtained healing in 88 per cent of their patients. They concluded that beneficial results were due to the maggot extract and not to the vaccine, since the vaccine alone proved ineffectual. ROBINSON and NORWOOD (*J. Bone and Joint Surg.*, 1933, 15, 409) are of the opinion that live maggots are necessary, since macerated maggots show no bacteriocidal properties when added to cultures. These authors point out that maggots ingest large numbers of bacteria,

bacteria being found in large numbers in the foregut while there is apparently a disappearance of organisms in the lower intestinal tract. In addition they express the view that favorable action due to maggots results from the ability of the larvæ to reach small recesses of the wound, removing bacteria and débris, and to a stimulating action which causes a thin serous discharge. This discharge assists in washing out large numbers of bacteria and assists in drainage of the wound.

To those who have witnessed the results brought about by the introduction of maggots in osteomyelitis, this form of treatment appears promising. The results reported thus far indicate that this method is on a sound basis. Whether the Orr treatment or the Baer treatment is the method of choice will depend largely on further study, since too short a time has elapsed to draw definite conclusions.

THERAPEUTICS

UNDER THE CHARGE OF

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The Presence of Estrogenic Substances in Bituminous Material.—Inasmuch as bitumen is known to be composed in part of fixed residues of fossilized animal life, and since estrogenic material has also been demonstrated in both the lower forms of animal life and plant cells, ASCHHEIM and HOHLWEG (*Deutsch. med. Wchnschr.*, 1933, 59, 12) studied a group of extracts obtained from various types of bituminous material by means of the several recognized biologic tests and found them to contain variable but significant amounts of estrus hormone. The extracts studied were derived from mineral oil, peat, soft coal and asphalt. These materials were demonstrated to contain from 400 to 10,000 mouse units per kg. of the native substance. Positive reactions were obtained by means of the Allen test, action on the uterus of castrated animals, on the mammary gland, on the cervical ganglion cells and upon the anterior lobe of the hypophysis. The significance of these findings for therapeutics is for the present left without comment by the authors.

A New Preparation Inhibiting Thyroid Activity in Grave's Disease.—About 2 years ago Blum demonstrated the existence of a substance in blood, apparently of hormonal nature, which possessed marked anti-thyroid activity. This property was demonstrable in biologic experiments as well as clinically by the use of large quantities of whole blood or even of preserved dried blood but proved objectionable and impracticable for clinical use. Further researches have lead to the preparation

of a highly purified extract of blood, called tyronorman. This preparation is standardized biologically, 1 unit being capable of neutralizing the activity of $\frac{1}{1000}$ mg. of iodine in the thyroid gland and it is further standardized biologically with reference to its power to reduce the basal metabolism in rabbits when raised by the administration of thyroid. The preparation is available in tablets containing 10 units per tablet. HERZFELD and FRIEDER (*Deutsch. med. Wchnschr.*, 1933, 59, 84) report upon the use of this preparation in 18 cases of Graves' disease selected from among those of extreme severity and in whom the usual operative procedures were felt to be too dangerous. They administered daily doses, ranging from 30 to 90 units, and observed a marked improvement in all but 2 of the patients. The improvement was rarely noticed until the second week of treatment but was usually rather prolonged, although subsequent administration of smaller doses were frequently necessary. The patients showed a reduction in heart rate, a progressive and marked fall in basal metabolism, a pronounced increase in weight and a rapid disappearance of the symptoms referable to the vegetative nervous system. Exophthalmos was also generally diminished, but the enlargement of the thyroid gland was not materially influenced. One of the two failures occurred in a patient whose condition was complicated by a tumor, the other in a patient who was not coöperative in carrying out the treatment. Although the treatment alone was fairly effective, it was found that the results of the administration of tyronorman were improved if the patient followed the restrictions in diet originally advocated by Blum, namely, the avoidance of all animal food and its derivatives of protein nature, of coffee, tea, nicotin and alcohol, limiting the diet thereby chiefly to fat and carbohydrates along with vegetables, fruits and an abundance of milk.

The Circulatory Actions of Commercial Liver Preparation.—KRAYER (*Deutsch. Med. Wchnschr.*, 1933, 59, 576) reports a series of pharmacologic studies on the circulatory actions of four well-known commercial preparations of liver used for the control of anemia, and contrasts them with the similar actions of a preparation known commercially as eutonon, which is a liver preparation reputed to have pronounced circulatory actions. The results of his experiments are striking in that they failed to reveal any significant circulatory action of eutonon on the heart-lung preparation while all of the other liver extracts exerted identical and marked effects. The actions observed were a pronounced increase in coronary blood flow, a marked stimulation of cardiac rate and a more or less significant reduction in the minute volume output of the heart. Despite the observations of these actions on the heart-lung preparation, the author emphasizes the fact that there is no pharmacologic reason for believing that any of these preparations may be regarded as therapeutically valuable in the treatment of any of the forms of cardiovascular disease.

Clinical Observation of the Reaction of Lecithin on Refractory Cases of Cardiac Failure.—Led by pharmacologic and physiologic experiments of other workers who showed the beneficial effects of the administration of lecithin in the restoration of the loss of phosphatids and cal-

cium from the exhausted heart, SCHEFF (*Zeitsch. f. Kreislauf.*, 1933, 25, 285) studied 5 patients intensively over a considerable period of time. His observations showed that the parenteral administration of fairly large doses of lecithin was invariably followed by a marked improvement in the efficiency of the heart and a restoration of its ability to respond to the administration of the usual cardiac stimulants, to which it had apparently become unresponsive. This effect of lecithin was further controlled by a fairly prompt return of cardiac inefficiency and loss of responsiveness when its administration was omitted. The author does not contend that lecithin itself is a cardiac stimulant but rather that it restores the physiologic state of the heart, thus permitting it again to respond to appropriate drug therapy.

PEDIATRICS

UNDER THE CHARGE OF
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Poliomyelitis: Comparison Between the Epidemic Peak and the Harvest Peak.—TOOMEY and AUGUST (*Am. J. Dis. Child.*, 1933, 46, 262) call attention to the synchronism between the peak of the epidemics of poliomyelitis and the peak of the harvest in an attempt to explain at least one method of transmission. They state that infantile paralysis need not be due necessarily to fruits and the like, but perishable foods might serve as one of the vehicles by which the disease is carried. Such a conception would explain the somewhat explosive and dispersive type of infection that occurs during the harvest peak. They feel that Aycock's "southern incidence curve" could be explained on the basis of an earlier harvesting date. The latter observer called attention to the fact that the incidence of this disease bears a resemblance to the incidence of typhoid fever. Kling called attention to its resemblance to dysentery. Its coincidence with gastro-intestinal disease is very apparent if one constructs a dysentery percentage curve from figures found in the Japanese Sanitary District report of 1929, with its peak in August and September. It can be seen that there is an obvious similarity between the curves of the incidences of poliomyelitis and dysentery. The typhoid curve of the same district was plotted, and confirmed Aycock's epidemiologic observations. Flies are a common carrier of typhoid and dysentery. Johnson detailed the number of flies that were caught weekly in various places in New York City. The elements of chance entered a great deal in this consideration, but when the figures were arranged and a curve plotted, it is interesting to note that the curve of the greatest number of flies occurred a little before the season of the greatest incidence of the disease. The handling of infected fruit or vegetables by infected people, the eating of infected fruits and vegetables by cattle with subsequent infection of milk, and the spreading of the infection from fruit to fruit by flies could serve to explain the spread of the disease and the incidence at this time of the year. To

this should be added Kling's claim of water as a possible source of infection. The curves plotted by the authors showed that the incidence curves of the disease followed closely the curves of the harvest of the perishable foods. The curves for other countries, while inferential approximations, bore a striking similarity to these curves. While they do not draw definite conclusions they remark on the fact that in their locality the peak of the poliomyelitic incidence curve should correspond so closely to that of the harvesting curve.

Preventing Loss of Weight in the Newborn.—KUGLEMASS, BERGGREN and CUMMINGS (*Am. J. Dis. Child.*, 1933, 46, 280) say that loss of weight in the newborn is sanctioned universally, but they claim that this is without physiologic foundation. They claim also that the newborn infant is markedly underdeveloped for the long duration of human gestation, and so requires continuous supervision for the prevention of potential pathologic changes. They observe that the neonatal growth gradient continues unaltered during the postnatal period according to the analysis of the transitional growth trends of the body as a whole as well as of its tissues and organs. Therefore they conclude that the initial loss in weight is necessarily extrinsic. Postnatal loss of weight does not occur in animals of any size, gestation period or scale in evolution, according to a survey of observations of veterinarians and others in contact with animals. The authors state that the initial loss of weight in the human newborn is the result of dehydration and semi-starvation, which conditions are unfavorable for the nutritional, physical and environmental adjustments besetting the newborn. The therapeutic procedures in the past for decreasing the loss of weight in the newborn were not successful because they were not based on the physiologic needs of the newborn, disturbed by the shock of birth. The initial loss in weight in the newborn can be prevented by the administration of a solution consisting of 6 per cent gelatin, 3 per cent dextrose and 0.5 per cent sodium chlorid at 2-hour intervals throughout the 24-hour period immediately after birth. The gelatin hydrates the blood and tissues, and it raises body heat by virtue of its specific dynamic action, and it reduces the clotting time of the blood. Dextrose brings the hypoglycemia of the newborn to normal. Sodium chlorid raises the initially low blood chlorid and favors hydration. The average loss of weight in newborn infants receiving the hydrating solution was 1.7 per cent as the irreducible minimum as compared with the average loss of 7 per cent in the controls. The characteristic clinical picture of the newborn is a result of birth shock, and is more effectively combated by the hydrating solution than by milk mixtures during the first 2 or 3 days of life. It was found that the total fluid intake of newborn infants properly conditioned to both bottle and breast was as much as twice that of the group receiving the routine nursery care. The method of preventing loss of weight in the newborn produces, in addition, the rapid disappearance of the so-called physiologic apathy, somnolence and stupor secondary to birth shock and the compensated acidosis universally present.

Endemic Cerebrospinal Fever in Childhood.—SHAW and THELANDER (*J. Am. Med. Assn.*, 1933, 101, 746) state that the progress of these

cases through the varying stages of infection presents many interesting possibilities for speculation regarding the pathologic physiology. The evidence is fairly conclusive that the entrance into the body is by the way of the respiratory tract. This is followed by an infestation of the blood stream scarcely equaled by any other bacterial infection, which in turn is followed by localization of the organism in the skin and in serous membranes of the body. The original focus of infection is usually of a minor nature, although sometimes it is grossly apparent. Actual empyema of the antrums of the ethmoid sinuses is described, but is not the rule. These observers have not seen nor found described such local changes in the bloodvessels, thrombosis or phlebitis of larger veins from which dissemination of infected emboli might result in the usual manner of producing a sepsis. Neither are secondary disseminating foci, such as heart valve lesions, the rule. When organisms are seen free in blood smears, they are found within cells or free in the plasma, and do not appear in bacterial clumps nor enmeshed in fibrin. The areas of skin localization present significant information. The marked skin eruptions tend spontaneously to regress, and following intravenous treatment they quickly and almost entirely disappear. This is not reconcilable with an embolic theory or with any mode of origin other than their production by a vascular toxin, which may be neutralized by an antitoxic effect of the serum. In meningeal localization, areas of perivascular inflammation first appear which are not unlike the early changes in the skin. Slight signs and symptoms of meningeal irritation sometimes accompanied the stage of sepsis even when meningitis did not develop. The original meningeal reaction is in the nature of a meningismus dependent on vascular changes rather than a response to bacterial infection of the spinal fluid. The evidence seems fairly convincing that the manner in which the organism gains unimpeded entrance to the blood, and thereafter affects distant tissues, depends on the action of an exotoxin or endotoxin which produces vascular changes of such a nature as to permit this massive ingress from a small original focus and in a similar manner permits egress to the tissues.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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The Rôle of the Streptococcus in Trichomonas Vaginitis.—So much has been written in recent years about the type of vaginitis in which the *Trichomonas vaginalis* is supposed to be the etiological factor that the contribution of HIBBERT (*Am. J. Obst. and Gynec.*, 1933, 25, 465) is of interest. He states that the *Trichomonas vaginalis* may be found in

the vaginal secretions of many women for long periods of time without producing an acute vaginitis. On the other hand, in a large percentage of cases having an acute vaginitis where the *Trichomonas vaginalis* exists, there is an associated predominant growth of a Gram-positive, non-hemolytic, short chain streptococcus present which is capable of producing an active vaginitis when not associated with the *Trichomonas*. He has found that by repeated vaginal application of a specific streptococcic bouillon filtrate the active growth of the organisms in the vagina ceases and the vaginitis subsides in spite of the persistence of the protozoön in the secretions. After describing the method of preparing the bouillon filtrate he states that the method of treatment of the patients was uniform. All other methods of treatment were suspended, all douches forbidden and the patient was allowed only one tub bath daily. In indicated cases repeated cauterization of the cervix was resorted to where cervicitis was present. The vaginal canal was dried with sterile cotton pledgets and a large cotton tampon, saturated with the bouillon filtrate, was packed against the cervix and allowed to remain in place for 12 hours, during which time the patient was advised to remain off her feet in order to aid in retaining the fluid in the vagina. The treatment was repeated 2 or 3 times a week until the vaginitis disappeared.

Relationship Between Ovarian Follicle Cysts, Hyperplasia and Uterine Myomata.—Although myomatous tumors of the uterus are the most common neoplasms of the female generative organs, their exact etiology remains unknown. After discussing the various theories pertaining to the histogenesis and etiology of these tumors, WITHERSPOON (*Surg. Gynec. and Obst.*, 1933, 56, 1026) presents evidence to show that the unopposed action of estrin (the ovarian follicular hormone) in the absence of corpus luteum influence is the cause of hyperplasia of the endometrium. Furthermore, he suggests that the unopposed action of estrin on the myometrium, if prolonged sufficiently, would result in fibromyomatous growths. This hypothesis is based on a study of 26 cases of hyperplasia of the endometrium, in which operation was done and the diagnosis as such was made from microscopic study and in which a second operation was performed for fibroids after an approximate interval of 4 years and 4 months, and also upon a study of 124 cases of fibroids, diagnosed microscopically. In this latter group the associated ovarian and endometrial findings present evidence which he believes adds support to a cause and effect relationship between ovarian follicular cystic formation, hyperplasia of the endometrium and fibromyomata of the uterus. Therefore, he advances an hypothetical conclusion that the unopposed action of estrin on the uterus results in immediate endometrial changes characterized by hyperplasia, and, secondly, in more latent myometrial changes in the nature of fibromatous growths. It is now believed by many observers that functional uterine hemorrhage which is dependent upon endometrial hyperplasia can be controlled by the use of anterior pituitary hormone which counteracts the effect of the ovarian follicular fluid. Reasoning by analogy, if this theory of Witherspoon be valid, the prophylactic use of anterior pituitary hormone should decrease the incidence of uterine fibroids.

OPHTHALMOLOGY

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The Fundus in Hypertensive Disease and Its Sequels.—SCHEERER (*Med. Klin.*, 1933, 29, 245) thinks that the initial stage in so-called "blood pressure disease" is the "spastic-atonie symptom complex of vasoneurosis" in which the arterial capillaries are narrowed and the venous dilated. When the spastic narrowing involves the arterioles also, the blood pressure rises. In either of these two stages closure of the central artery or vein of the retina can occur without the presence of organic changes. A continuance of the spastic narrowing leads to organic changes in the retinal arterioles and, if nephrosclerosis occurs also, the terminal picture of albuminuric retinitis may be seen. The characteristic retinal change in this primary type of hypertension is contraction of the arteries with relative dilatation of the veins. In nephrogenic hypertension, by contrast, the retinal veins are narrowed as well as the arteries. Albuminuric retinitis may be the terminal picture in this type of hypertension also. Arterial and venous closures do not occur. In the senile type of arteriosclerosis without rise of blood pressure, narrowing of the retinal arteries and veins occurs with disappearance of many of the smaller vessels, obliteration of capillary beds, and thinning of the retina. In this type, arteriosclerotic closure of the central artery or vein may occur and senile macular degeneration is frequent.

On Changes of the Optic Canals in Cases of Intracranial Tumor.—LYSHOLM and OLIVECRONA (*Acta chir. Scand.*, 1932, 72, 197) studied the roentgenograms of the optic canals in their cases of tumors in the chiasmal region with special reference to their aid in making a differential diagnosis of the type of tumor present. Changes in the optic canals were observed in gliomas of the optic chiasm, pituitary adenomas, and cholesteatomas of the suprasellar region. The changes present in association with gliomas of the optic chiasm and with suprasellar cholesteatomas were quite similar and consisted of dilatation of one or both optic canals with enlargement of the sulcus chiasmatis but without destruction of the walls of the canals. In 2 cases of chromophobe adenoma of the pituitary, in addition to dilatation of the optic canals, considerable destruction of the walls of the canals was present in association with rather extensive changes in the sella. A marked unilateral dilatation of the optic canal was observed in a case of tumor of the intra-orbital portion of the optic nerve. It is suggested that a more routine study of the optic canals in chiasmal lesions may bring out further differential diagnostic points.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Effects of Radiation on Allergic Nasal Mucosa.—Inasmuch as the therapeutic results of vasomotor (hyperesthetic) rhinitis by medical, surgical and allergic methods have been frequently disappointing, a consideration of the known effects of radiation on normal and pathologic nasal mucosæ suggested to BERNHEIMER and CUTLER (*Arch. Otolaryngol.*, 1932, 16, 561) the use of radium to correct the local pathologic processes encountered in allergic nasal conditions. Accordingly, 40 patients with hyperesthetic rhinitis were irradiated—all of whom had experienced periodic paroxysms of sneezing followed by profuse rhinorrhea and nasal block, which occurred independently of season or climate. The intranasal structures were pale and waterlogged. Of the 11 persons yielding positive cutaneous reactions to various allergens, none had been benefited by allergic therapy. Only temporary improvement had followed numerous surgical procedures in 29 of the 40 cases. All the irradiated patients were free of polypi and secondary nasal infection. After topical cocainization a capsule containing 25 mg. of the radium element—total filtration being 0.5 mm. of silver and 1 mm. of brass—was placed in the middle and inferior meatuses of each nasal chamber for 2 hours—a dosage of 200 mg. hours. The morphologic and clinical response was uniformly striking—all the patients being appreciably benefited during the first 6 months. In a second communication (*Arch. Otolaryngol.*, 1933, 17, 658) the same authors report that after 1 year, 52 per cent of these 40 irradiated patients were symptom-free; 20 per cent no longer had nasal block or watery discharge, although sneezing persisted in a moderate degree; 8 per cent were fairly comfortable; 10 per cent had received but little relief, and 10 per cent had not been benefited. No untoward sequelæ from their method of irradiation were observed. The authors frankly state that they regard the procedure as an empiric one and offer it solely as a useful adjunct in the many cases in which specific therapy had failed to correct the allergic state.

RADIOLOGY

UNDER THE CHARGE OF

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Actinomycosis of the Spine.—Actinomycosis is widely distributed over this country and is especially prevalent in the upper Mississippi Valley and the Northwest. Almost every region of the body has been

known to be affected, but the spine is one of the rarest sites known. TABB and TUCKER (*Am. J. Roent. and Rad. Therap.*, 1933, 29, 628) report an instance in a man aged 33. Following a proved actinomycotic infection of the neck, numbness and paresis of the arms with pain in the back developed. The roentgenogram disclosed a perivertebral abscess and marked destruction of the 10th and 11th dorsal vertebræ, which, however, had not collapsed. A roentgenogram of the lungs also disclosed numerous foci in the upper half of the left lung, and actinomyces were found in the sputum. From a review of cases reported, Tabb and Tucker conclude that this disease usually attacks two or more vertebræ, that it attacks any part of the vertebra without preference for the body, and that the intervertebral spaces show little if any narrowing. Large perivertebral abscesses form early. Usually the lung is also affected when the spine is involved. Absence of collapse or kyphosis, despite extensive destruction of the vertebræ and the intact intervertebral spaces, aid in distinguishing actinomycosis from tuberculosis.

Hypertrophy of the Pyloric Muscle in Adults: A Distinctive Roentgenologic Sign.—Lesions at or near the pylorus are seldom difficult to discover with the Roentgen ray, but they are extraordinarily hard to identify specifically, for carcinoma, benign ulcer, syphilis and hypertrophy of the pyloric ring, which are the most common lesions here encountered, produce perplexingly similar manifestations. During recent months, however, KIRKLIN and HARRIS (*Am. J. Roent. and Rad. Therap.*, 1933, 29, 417) have noted a roentgenologic phenomenon which appears to be peculiar to pyloric hypertrophy. The most obvious direct manifestation of uncomplicated hypertrophy is elongation of the pyloric canal. Not rarely the canal is eccentric in relation to the bulb. A definite mass corresponding to the defect cannot be felt. Hyperperistalsis is observed occasionally; gastric dilatation and retention of residue from the six-hour meal are rare. Thus far none of these signs is characteristic of pyloric hypertrophy, for similar manifestations are seen often in early scirrhus carcinoma, early syphilis, and prepyloric ulcer with spasm. But in pyloric hypertrophy Kirklin and Harris have noted a crescentic indentation of the bulbar base. It was evident in a series of 81 cases when the bulb was plainly depicted, accords with the morbid anatomy and has not been observed by the authors in other states of health or disease.

Diathermy Test for Sugar and Albumin in the Urine.—Because the present method of testing urine qualitatively for sugar and albumin is slow, messy and hence often neglected, KIMBLE (*Arch. Phys. Therap., X-ray, Rad.*, 1933, 14, 237) has developed an electric device which eliminates these objections. The instrument consists of two small plates, insulated from each other, and connected through a shaft and cord to the terminals of a diathermy machine. It is designed to fit into any standard 20-cc. test tube. To test for albumin the tube is filled one-third full of urine, and a few drops of acetic acid added. The instrument is inserted and about 2000 ma. of current turned on. Albumin present is quickly coagulated and a white line appears between the terminals in from 2 to 5 seconds. To test for sugar 1 cc. of alkalin

bismuth subnitrate is added to the urine, and the same amount of current is employed. In a few seconds the solution between the two plates boils and is allowed to boil for $\frac{1}{2}$ minute. If any sugar is present a black ring appears between the terminals.

Roentgen Diagnosis of Bone and Joint Tuberculosis.—Although he considers it obvious that criteria used in the roentgenologic diagnosis of tuberculosis are subject to diversified exceptions which make accurate interpretation extremely difficult, POMERANZ (*Am. J. Roent. and Rad. Ther.*, 1933, 29, 753) enumerates the chief manifestations as follows: Synovitis and periarticular swelling, bone atrophy or sclerosis, bone production and destruction in epiphysis and metaphysis, narrowing of joint space, sequestration and the presence of cold abscesses or sinuses. Synovitis, periarticular swelling and bone atrophy are common to all arthritides and are only of corroborative value in the diagnosis of tuberculous arthritis. Sclerosis and production of bone occur in tuberculosis even in the absence of mixed infection, and, conversely, when sinuses exist bone production may be absent. Wedge or cone-shaped lesions are usually tuberculous. Kissing sequestra are common in tuberculosis. Narrowing of a joint space which occurs late in an infection, despite associated destructive changes, is strong presumption of the existence of tuberculosis. Complications, such as kyphosis, subluxation and sinus formation, occur in tuberculosis as well as other arthritides. Roentgenologically the presence of a cold abscess specifically identifies the process as tuberculous.

Roentgenologic Studies of the Intervertebral Disc.—According to COMPERE and KEYES (*Am. J. Roent. and Rad. Ther.*, 1933, 29, 774), the nucleus pulposus, although genetically derived from the notochord, is not a vestigial remnant but an essential anatomic entity. It acts as a hydrodynamic ball bearing and axis of motion. Injury of the nucleus pulposus, whether primary or secondary to injury or to disease of the adjacent vertebral body, cartilage plate or annulus fibrosus, results in a decrease in normal function of the spine. Loss of nucleus pulposus material as a result of trauma or disease is probably one of the frequent etiologic factors of pain in the back and disability. Evidence indicates that degenerative or hypertrophic arthritis of the spine may result from loss of the nucleus pulposus, with subsequent erosion and narrowing of the fibrous and cartilaginous portion of the intervertebral disc. Prolapse of the nucleus pulposus into the spongiosa of the vertebral body is regarded by Schmorl as the commonest lesion of the spine. As a result of pressure by the weight of the body and by the tone of the muscles and ligaments, the nuclear material is extruded into the spongy bone, and the latter reacts to the invasion. The semifluid material is transformed into a cartilaginous nodule and the bone about it becomes sclerosed. If a large portion or all of the material is extruded the cushioning effect of the disc is lost, weight must be borne in part by the annulus fibrosus, and the intervertebral disc becomes thinner or disappears. As a result the adjacent vertebræ may become sclerosed and the lipping and spurs characteristic of osteoarthritis of the spine will be apparent in the roentgenogram.

NEUROLOGY AND PSYCHIATRY

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Lumbar Punctures in Psychotic Patients.—EPSTEIN and LOTT (*J. Nerv. and Ment. Dis.*, 1932, 76, 593) state that the performance of lumbar punctures in psychotic patients is greatly facilitated by the use of sedatives, such as sodium amytal and nembutal. With the use of these sedatives, better coöperation is obtained for the lumbar puncture. Many of the difficulties in handling psychotic patients are overcome. Within an hour after the administration of the drug the patients are, as a rule, in a somnolent state, which may last from 4 to 8 hours. In this condition the patients offer no objections to the test and the element of fearfulness and anxiety is reduced to a minimum. There is little complaint of pain during the puncture. The patients are very drowsy afterward and are willing to lie on their backs in bed for the next twelve hours. No unpleasant memories of the procedure exist and consequently there is no opportunity for the wholesale dissemination of the "horrors" of the spinal test and engendering fear and antagonism toward the procedure among other patients. Another important advantage resulting from good coöperation between patient and the operator is the occurrence of fewer bloody (traumatic) taps.

The Depressive Reaction Types.—HARROWES (*J. Ment. Sci.*, 1933, 79, 325) classifies the depressive reactions into the following groups: (1) Depressive reactions; (2) autogenous reactions; (3) recurrent depressions; (4) psychoneurotic depressions; (5) depressions with aversion; and (6) involutional types. The reactivity should be measured in terms of the patient's reaction to stimuli during the illness as well as the reaction to the etiologic factors. In the reactive group, besides the formal depression, were a lack of concentration, loss of interest, insomnia, loss of thought capacity, heightened sense of effort, headaches, forgetfulness. Self-accusatory trends were not prominent. The etiologic factors in the 14 cases reviewed were: sex and marital difficulties, 11 cases; work failures and difficulties, 2; and physical illness in 1. The more cumulative the onset the more prolonged the psychosis. The more topical the affect, the less severe the psychosis. Constitutional and hereditary factors played a definite rôle, along with personality features such as unimaginativeness, materialism and rigidity. The reactive cases did not show any uniformity in the diurnal variation

of severity of symptoms, some being better in the evening and others in the morning. The retardation was not marked.

The autogenous depression presents characteristic differences from the reactive group which indicates a more sweeping type of disorder. The reactive group might be called partial reaction, and the autogenous group total reaction. Remorse and guilt ideas were more prominent and the affect embraces and involves more of the total personality of the individual. There is some distortion and a rut formation which is not seen in the reactive cases. A large proportion of the autogenous depressions showed recurrences.

The recurrent cases showed characteristic features, especially the tendency of attacks to become more severe as age advances. Otherwise, the picture presented has the same features as the single-attack autogenous depression, with the exception that there is more distortion and more rigidity present with evidence of an apprehensive, worrying disposition indicative of a more constitutionally depressive set than in simple cases. Guilt ideas were most prominent as well as agitation and tendency toward hypochondriasis.

The psychoneurotic depression usually developed on the basis of a neuropathic constitution with a characteristic makeup in which vaso-vegetative and neural disorders, including tachycardias, asthenias, sweat phenomena, asthma, tics, bed-wetting and nail-biting, were present. All degrees of anxiety were noted. The depression in this group is essentially topical and tends toward chronicity.

In the depressions with aversion definite paranoid trends were prominent along with the restriction of general interests and deterioration of affective response in any other direction. There is a reversal of the guilt component, and the presence of a rigid, dominating, obstinate personality-set. The prognosis in this group is poor.

The involutional depression with a well known syndrome of peevishness, hypochondria and nihilistic ideas, and restriction of affect were most typical. Sudden onset, impulsive suicidal attempts were frequently noted.

In summarizing the depressive reactions, there appears to be the following groups: (1) Where a real life-situational, dynamic cause can be seen; (2) another where the cause is more entirely constitutional; (3) a group with a special affectivity handicap in the form of a psychosis; (4) a group with aversion, where the prognosis is bad; and (5) a special type of agebound depressions with a better prognosis than might be expected. The prognosis in the reactive group seems very much a question of balancing the trauma and the personality assets. In the autogenous cases the personality alone can be focused on. Emphasis is laid on rigidity of the personality as an ominous sign. The type of onset—cumulative or catastrophic—and the extent to which the affect is bound to the etiologic topics are of prognostic significance.

EDITORIAL COMMENT.—This is a most excellent article. Perhaps simpler classifications would be of value, such as the one proposed by Gillespie consisting of two main groups—the reactive and the autogenous, with a subgrouping to include involutional cases.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Agglutination Experiments as Evidence of the Diversity of Non-hemolytic Streptococci.—CROWE (*J. Inf. Dis.*, 1933, 52, 192) suggests four criteria for the differentiation of various races of bacteria: (1) Cultural and microscopic characters; (2) disease producing characters; (3) special morphologic and biochemical characters; (4) serologic characters. The author's medium demonstrates cultural and gross morphologic characters. The medium is chocolate-colored, glassy and opaque, and is composed of 75 per cent of heated, defibrinated blood. Differences in the amount of H_2O_2 produced are shown by the degree of greenish discoloration surrounding the colonies. The microscopic characters are variable according to environment, and, therefore, are of little value except under exactly similar conditions of growth. The second criterion—disease producing characters—is not sufficient to distinguish microbes, since different organisms are responsible for the same clinical conditions. The third criterion is based on special media and fermentation characters which are not wholly reliable. By agglutination tests with monovalent rabbit serums, criterion 4, it is shown that certain streptococci differing on cultural characters, but similar in fermentation are heterologous in type, indicating that they are definitely distinct organisms since two of three criteria are satisfied. The differences between the varieties of non-hemolytic streptococci cannot reasonably be ascribed to mutation but are to be considered fundamental.

Syphilis of the Pulmonary Artery.—KARSNER (*Arch. Int. Med.*, 1933, 51, 367) reviewed the literature on syphilis of the pulmonary artery and reports a case. Peck had previously analyzed the cases of syphilis of pulmonary artery up to 1927, accepting only 12. The author collects 16 cases. His case presented difficulty clinically, in that there was reasonable evidence of syphilitic aortitis, but the presence of a to-and-fro murmur in the right carotid, absence of pulse in arteries of the arm and a systolic murmur heard in the pulmonic area presented a confusing picture. After autopsy, further study of previous roentgenograms revealed a shadow at the right hilus, indicative of dilatation of the right pulmonary artery. At autopsy the significant findings were marked syphilitic arteritis of the arch of the aorta and the main trunk of the pulmonary artery. There was a fusiform dilatation and small saccular aneurysms of the aorta with syphilitic arteritis of the three branches from the arch. The innominate and subclavian arteries were completely thrombosed and recanalized. The main pulmonary

artery presented a fusiform dilatation, with dilatation of the right branch and thrombosis with recanalization of the left. Microscopic evidence was definitely that of a specific process, presenting the productive cicatricial syphilitic lesions as seen in syphilitic mesaortitis. The author does not believe this process to have spread from the aortitis because of the part of the aorta in closest contact with the pulmonary artery was free from pathologic lesions.

Selective Action of Crystal Violet and of Brilliant Green on Bacteriophages.—For their experiments WELLS and SHERWOOD (*J. Inf. Dis.*, 1933, 52, 209) used six lytic principles, two for Gram-positive bacteria and four for Gram-negative bacteria. The mixtures of dye and bacteriophage were made in dilutions of 1 to 2500 to 1 to 10,000, and incubated at 37° C. The lysis against Gram-positive organisms was found to be inhibited by crystal violet in all dilutions within 48 hours. The lytic agents against Gram-negative organisms were never inhibited above 1 to 5000. The inhibitive property of brilliant green was extremely variable, but distinct with one phage of colon bacillus in particular. After incubation the activity of the phage was tested in high dilutions, *i. e.*, above that at which the dye was inhibitive on bacteria. The demonstration suggests that there is a correlation between the selective action of crystal violet on bacteria and their respective phages.

Desiccation and Preservation of Infectious Laryngotrachitis Virus.—A method for the preservation of virus in tracheal exudates by drying is described by GIBBS (*J. Bact.*, 1933, 25, 245). The desiccation of tracheal exudate *in vacuo* preserves the virus indefinitely because the moisture necessary for bacterial decomposition and the oxygen essential for oxidation and enzyme action are removed. The material is kept at a low temperature just above freezing until completely dehydrated, and protected from air, moisture and direct sunlight. A large desiccator is used and is sealed with a mixture of gum rubber, paraffin and vaseline. Acid phosphoric anhydrid is used as dehydrating agent. The air is evacuated to a vacuum of 300 microns mercury daily for 4 or 5 days, being kept in the ice box in the intervals. The tubes of exudate are then sealed with paraffin and kept in the ice box. Three strains of virus were tested; those desiccated at less than 300 microns were preserved not more than 1 year, while those treated at more than 300 microns were virulent up to 450 days.

Sclerosis of Pulmonary Artery and Arterioles.—SOKOLOFF and STEWART (*Arch. Int. Med.*, 1933, 51, 413) report a case of sclerosis of pulmonary arteries. Their record includes a 7-year period of observation of the patient, and a careful analysis of the case, in which they excluded the possibility of syphilitic infection by clinical, laboratory and pathologic investigations. The clinical diagnosis was not made until late in the disease, when the typical sign of Ayerza's syndrome became evident. Postmortem examination revealed a dilated and hypertrophied heart on both sides, with passive congestion and anasarca present throughout the body. The pulmonary artery and its branches

presented interesting features. Flat, grayish, firm plaques were seen, increasing in frequency toward the periphery, producing marked sclerosis of this arterial system. They suggest three pathogenic factors: (1) An attack of influenzal pneumonia 1 year before the onset of symptoms is possibly of some significance; (2) the patient received repeated injections of epinephrin to relieve periodic attacks of asthma, most of which were, however, unsuccessful; (3) the presence of an old fracture of rib, which might have caused local injury or stimulation of nerves resulting in the above lesions. They review experimental work to support each one of these factors.

HYGIENE AND PUBLIC HEALTH

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Lobar Pneumonia in Massachusetts: Methods and Results of Pneumococcus Type Determination, 1931-1932.—According to HEFFROM and VARLEY (*Am. J. Pub. Health*, 1932, 22, 1230), pneumococcus typing is being requested by increasing numbers of physicians in Massachusetts. During the past winter all 32 (Cooper) types of pneumococci excepting Types XXV and XXXII were found. There was no especial geographical distribution evident of any of the types found. Multiple cases of lobar pneumonia occurring in the same family at approximately the same time were very uncommon. The Krumwiede, Sabin and tube agglutination methods of typing were and still are largely used, and were found to be over 99 per cent accurate when definitely positive. The Sabin method of typing has given a greater number of accurate positive typings in a shorter period of time than any other method studied, and is a method readily learned by technicians inexperienced in this work. Of 789 specimens typed at the State Bacteriological Laboratory during the 11 months, September 1, 1931, to July 31, 1932, the type of pneumococcus found was checked in 94.6 per cent of the cases by a second method of typing or from a culture of the organism. The various sub-types (Types IV to XXXII) were found more frequently during the 6 winter and spring months, December to May, than during the warmer months. In view of the results to date, and until conclusive proof to the contrary is obtained, it is felt that every type determination done by the Krumwiede, Sabin or tube agglutination method should be checked by some other method of typing. Typing the organism obtained from cultures of the mouse heart's blood affords the most valuable means of checking.

Plasmochin in Malaria Prevention.—The results of two experiments conducted by BAKER and GILL (*U. S. Pub. Health Rept.*, 1932, 47, 2245), covering 2 consecutive years, suggest that plasmochin compound in a dosage of 1 to 2 tablets per week (each tablet containing 0.01 gm. plasmochin and 0.125 gm. quinin sulphate), when administered to all the inhabitants of a district, will materially lessen the incidence of malaria. Such a dosage is both safe and convenient. If further experience confirms these results, it would seem that a valuable addition has been made to the present methods of malaria control, which therapeutic control may be further enhanced through scientific chemical study of the potentialities embraced in plasmochin.

The Fernald Plan for the Examination of Retarded School Children.—DAYTON (*New England J. Med.*, 1932, 207, 913) states that the present high position which Massachusetts occupies in the care of the mentally deficient is due largely to the pioneer work of Dr. W. E. Fernald. Over 30 years ago he realized the urgent need for public recognition of the problem of mental defect and the necessity for early diagnosis of cases showing mental retardation. His first plan was the creation of an out-patient department. Later, he conceived the thought of projecting the out-patient examination into the public school system, and by means of a traveling clinic to visit each school, conducting a comprehensive examination of the retarded children therein. The first of these units was inaugurated in 1914, and the second in 1917. The "Ten-point Scale Examination" presents a detailed picture of the retarded child, giving the sum total of his characteristics and reactions apart from his intelligence. The personnel of the traveling clinic unit consists of a psychiatrist, a psychologist and a social worker. In addition, the school provides a school teacher, a school nurse and a visiting teacher who assist in certain phases of the examination. Since the inauguration of the school clinic system in 1914, a total of 51,205 examinations of retarded children have been conducted. Approximately 41,000 of this total are first examinations, and 10,000 are reexaminations. These figures show the magnitude of the problem of the retarded children within the public schools, and demonstrate the volume of work which has been accomplished by the traveling school clinics.

Further Attempts at Experimental Infection of Man With a Bovine Strain of *Brucella Abortus*.—MORALES-OTERO (*J. Inf. Dis.*, 1933, 52, 54) states that in spite of the little prevalence of spontaneous human infection in regions where infectious abortion in cattle is common, a fever in man similar to undulant fever may be produced by artificial inoculation with cultures of *Br. abortus*. His previous experiments left no doubt that strains of porcine origin in particular are decidedly pathogenic for man. They not only cause infection when injected through abraded skin, but are also able to penetrate through the gastro-intestinal canal when fed in sufficient quantity. In contrast to this, it has not been possible to produce human infection by feeding a strain of bovine origin, isolated in Puerto Rico. A family consisting of 3 members volunteered to ingest for 6 weeks the infected milk of a

cow suffering from infection with *Br. abortus*. At the end of this period, none of the members had at any time shown any symptoms of the disease, and their blood cultures and blood agglutination tests remained persistently negative for *Br. abortus*. Two other volunteers, inoculated, 1 through normal and the other through abraded skin, with a strain isolated from infected cow's milk, presented no symptoms of the disease, and their blood cultures were persistently negative for *Br. abortus*. In the blood of the latter of the 2 persons a transitory positive agglutination of the organism (in a 1 to 40 dilution) was observed during the third and fourth weeks of the experiment. Hence, the pathogenicity for man of bovine strains must be low, an assumption supported by the wide distribution of infectious abortion in cattle with no corresponding spontaneous occurrence of undulant fever in the human being. On the other hand, reports from southern Rhodesia and Denmark seem to indicate that human infection in those countries is frequently due to the bovine type of bacillus. Further work is necessary to study the various pathogenic and non-pathogenic races of *Brucella* and to determine if there are any factors that might lead to an exaltation of virulence in those that are normally considered non-pathogenic.

Typhus Fever.—CEDER, DYER, RUMREICH and BADGER (*U. S. Pub. Health Rep.*, 1931, 46, 3103) were unable to transmit typhus to animals by direct biting of fleas, but succeeded by the inoculation of crushed fleas and by the use of fresh feces. DYER, WORKMAN and RUMREICH (*Ibid.*, 1932, 47, 2370) report the recovery of typhus virus from rat fleas in different parts of the world. In the present report, the rats were trapped in the United States on premises where cases of endemic typhus in man had occurred. The virus was recovered from rats by passing through guinea-pigs. Identification was completed by various pathologic and biologic tests.

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ORIGINAL ARTICLES.

STUDIES IN DIABETES MELLITUS.

I. CHARACTERISTICS AND TRENDS OF DIABETES MORTALITY*
THROUGHOUT THE WORLD.

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INSULIN was discovered scarcely more than 10 years ago and, within a year following its discovery, its efficacy in the treatment of the disease was demonstrated beyond doubt. Insulin changed the outlook of the average diabetic patient almost overnight. It freed him from the restricted life of the chronic invalid and often restored him to an active career. The diabetic child ceased to be a victim marked for death; insulin enabled him to join his fellows in school and in play; it gave him the prospect of growing to manhood, of becoming a useful member of the community. To the medical profession, insulin came as an enormous boon: the diabetic patient

* Throughout this article the diabetes death rates are computed per hundred thousand and unless otherwise mentioned.

can now be brought safely through serious illnesses and other emergencies requiring surgical intervention which hitherto were likely to prove fatal.

Yet today, the recorded mortality from diabetes is reaching levels never before attained. With the mortality rates now prevailing, 26 out of every thousand girl babies will eventually succumb to the disease and 15 out of every thousand male infants. In but 10 short years, the probability at birth of eventually dying from diabetes has increased over 50 per cent for female infants and 15 per cent for male infants. Fifty years ago deaths from diabetes were infrequent. The disease was a relatively minor cause of death. Even at the beginning of this century it was twenty-seventh in rank among the causes of death in this country. In the last three decades it has advanced to the tenth position in importance. Indeed, among females it is ninth in rank at all ages, and seventh at ages 45 and over. At these older ages, fewer women die of tuberculosis than of diabetes.

Diabetes has thus become a disease of major importance and for reasons which will appear later, its importance is increasing rather than decreasing. The amazing progress that has been made in its diagnosis and treatment has not stemmed the rising mortality from diabetes. This is hard, not only for the general public to understand, but for many in the medical profession also. The time is ripe, therefore, for a careful and thorough survey of the diabetes situation.

The primary aim of the authors is to show, in this and the papers which will follow, the great improvement in the prognosis of diabetes, and how this improvement may be measured. We shall also deal with the incidence of the important elements in the etiology of the disease, the complications of the disease, and the influence of these factors on the prognosis. We shall also try to discover what means will be most effective in bettering the outlook for those who have acquired the disease, and what is even more important, what measures may be evolved for cutting down the fast growing number of new cases. Our analysis of the diabetes situation will be critical and largely statistical. We shall deal with two main sources: first, the mortality data on the disease throughout the world and next, an analysis of the carefully compiled records of one of the authors (E. P. J.).

The first paper in this series presents data on the mortality from the disease.

The Increasing Importance of Diabetes in the United States. The annual toll of diabetes in the United States is now close to 28,000, if it does not already exceed that number. In 1932, there were actually 26,298 deaths from the disease in the Registration Area of this country, in which live 96 per cent of the population. The increase in the diabetes death rate this year (1933), which other

sources indicate has taken place, has probably carried the number beyond the 28,000 mark.

The 26,298 deaths from diabetes in 1932 were 2.0 per cent of all deaths in that year. If we disregard deaths from accidents and congenital conditions in the newborn, diabetes advances from ninth to seventh in rank. It will be interesting to compare the death rates from diabetes with those of the other leading causes of death (Table 1).

TABLE 1.—DEATH RATES FOR SPECIFIED CAUSES OF DEATH IN 1932, SHOWING RANKING ORDER OF DIABETES AS A CAUSE OF DEATH. ALL AGES, UNITED STATES REGISTRATION AREA.

Cause of death.	Death rates per 100,000.
All causes	1090.0
Diseases of the heart	209.5
Influenza and pneumonia	107.8
Cancer	102.2
Nephritis	87.3
Cerebral hemorrhage, embolism and thrombosis	83.4
Accidents	71.3
Tuberculosis	63.0
Congenital conditions	53.2
Diabetes	22.0

The growing importance of diabetes is made manifest by examining mortality data over a period of years. For comparable data on a national scale we are limited to the Death Registration Area of 1920. In this area, diabetes was tenth in importance in 1930, accounting for 20,234 deaths (1.8 per cent). Only 5 years before that the diabetes deaths were only 1.5 per cent of all deaths and in 1920, diabetes was twelfth in rank and caused only 1.2 per cent of all deaths.

At ages over 45, diabetes was eighth in importance in 1930. In that year, 2.4 per cent of all deaths at these ages was charged to it, as compared with only 1.9 per cent a decade before. Among white females over 45, the importance of diabetes has grown even more rapidly. In 1930, it was seventh in rank among the causes of death of older women, accounting for 3.4 per cent of the deaths. Diabetes had moved up from the eighth position in 1920, and the number of deaths had increased from 2.8 per cent of the total in 1925 and 2.4 per cent in 1920.

In older and more settled portions of the country, the disease assumes even greater importance. In the State of Massachusetts, diabetes was ninth in rank in 1930, but only thirteenth in 1910. Among females, at ages 40 and over, it was seventh in order of importance of the causes of death in 1930. This disease accounted for 2.1 per cent of all the deaths in that State in 1930 and for 3.5 per cent of the deaths of women at ages 40 and over. Twenty years before that, only 1.1 per cent of all deaths and 1.9 per cent of deaths of women at ages 40 and over were due to the disease.

The Comparative Mortality from Diabetes in the United States and Other Countries. The United States has a higher death rate from diabetes than any other country in the world—22.0 in 1932. To the north of us, in Canada, the rate in the same year was only 12.8, or less than two-thirds of ours. In England, too, the death rate from diabetes is much lower than in the United States, only 14.5 being recorded in 1931. The highest mortality from diabetes outside the United States is found in the Netherlands which in 1931 had a rate of 17.7. The next highest is Denmark, with a rate of 15.9 in 1931.

Examination of Table 2 shows that in the countries of Northern and Western Europe, diabetes death rates are not much different from those prevailing in England. The Latin countries experience a much lower mortality from the disease. In Italy, for example, the death rate for 1930 was only 8.2; in Spain, only 9.4 in 1929 and in Cuba, 5.1 in 1926.

TABLE 2.—DEATH RATES FROM DIABETES MELLITUS IN LEADING COUNTRIES OF THE WORLD.

Country.	Death rate per 100,000.
United States ¹	22.0
Netherlands ²	17.7
Denmark ²	15.9
New Zealand ¹	15.7
Union of South Africa ³ (European population only)	15.7
Prussia ⁴	15.3
Australia ¹	15.3
England and Wales ²	14.5
Scotland ²	13.6
Sweden ³	13.1
Canada ¹	12.8
Norway ³	10.8
Switzerland ²	10.4
Northern Ireland ²	9.6
Spain ⁴	9.4
Italy ³	8.2
Irish Free State ²	8.2
Czechoslovakia ³	8.1
Cuba ⁵	5.1
Japan ³	3.5

1932,¹ 1931,² 1930,³ 1929,⁴ 1926.⁵

The data already quoted relate to the white race. For the other races of the world, data are not very extensive nor reliable. For the yellow race, the only national data available are for Japan. In that country, diabetes is a relatively infrequent disease. In 1930, its death rate was only 3.5, or less than one-fifth of the rate in this country. Negroes in the United States have a much higher mortality. In 1929 their death rate was 12.7. The diabetes death rate of the American Indians in this country was 5.7 in the 3 years, 1927 to 1929, that is, much lower than for either the whites or negroes. The Chinese residing in this country had the extremely high rate of 32.3 in the same period, but their high mortality is largely due to the abnormal age distribution of the group. The Japanese living in this

country have an extremely low rate from the disease, only 2.8 in 1927-1929. New and more extensive data should explain this wide difference in diabetes mortality between the Chinese and Japanese in this country. New light on the problem can be sought in the hospital statistics of the two mother countries.

The Rising Trend in Diabetes Mortality. The death rates from diabetes have been rising steadily over a long period. This increase is world-wide. It is apparent not only in almost all civilized countries, but is found uniformly in local areas within these countries. Statistics for the United States do not represent the experience for

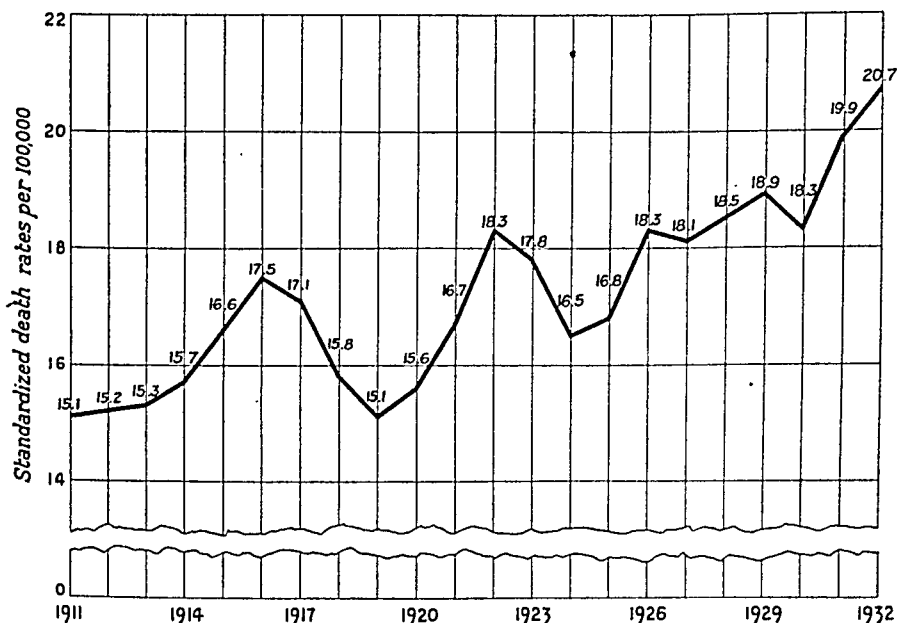


CHART I.—Diabetes death rates at all ages, 1 to 74. Metropolitan Life Insurance Company, Industrial Department, 1911-1932.

the country as a whole, but for the last 20 years we have a good cross-section represented by the families of wage earners insured in the Industrial Department of the Metropolitan Life Insurance Company. These families live almost entirely in the cities and towns of the United States and Canada and form such a large proportion of the communities in which they live that the carefully compiled mortality record that has been kept of them is an accurate index of mortality in this country.

The upward swing of the mortality from diabetes is clearly seen in Chart I which shows the death rates in these wage earning families during the 22 years ending in 1932. These death rates have been adjusted to eliminate changes in the age, sex and color composition of this population. The highest diabetes death rates have been recorded in recent years. The maximum rate, 20.7, was

reached in 1932, and thus far in 1933 the rate is higher than for the corresponding part of any earlier year. These peak rates are the culmination of a fairly steady advance in the death rate from the disease since 1924 when it was only 16.5. Thus, in the relatively short span of 8 years the death rate from diabetes rose 25.5 per cent.

The rise in these last few years is only the continuation of a broad advance which was evident even in the early years of our experience. Over the whole period 1911 to 1930 the increase amounts to 0.17 deaths per annum. This broad upward trend in diabetes mortality was interrupted at two points. The first time covered the later years of the World War and those immediately following the War when in all likelihood it was influenced by the restrictions on the use of food-

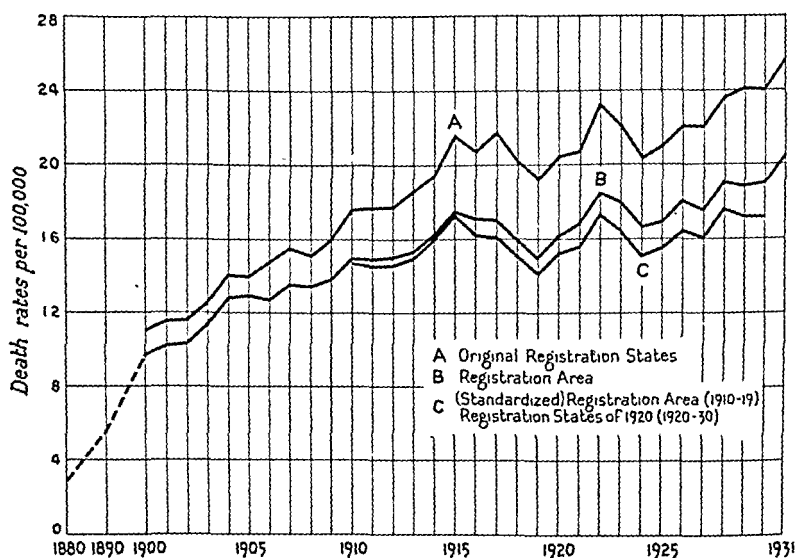


CHART II.—Diabetes death rates in the United States, 1880-1931.

stuffs through government regulation and by high prices. In part, the reduction in mortality during these years may be an artifact, because proper registration of deaths from the disease was affected by the diversion of large numbers of physicians into military service. The second interruption to the upward trend of diabetes mortality was in the years immediately following the introduction of insulin treatment.

The rise in diabetes mortality was at first moderate, reaching its first small peak of 17.5 in 1916, a rise of but 15.5 per cent from 1911-1912. Following this the death rate dropped to 15.1 in 1919. From the low point in 1919, the mortality rose rapidly reaching another peak, 18.3, in 1922. In the latter part of 1922, insulin which had been discovered the previous year by Drs. Banting and Best was introduced on a commercial scale for use by physicians.

Its effect on diabetes mortality was immediate and the death rate for 1923 showed the first decrease since 1919, followed by a further fall in 1924. In that year the rate was 16.5, or 9.8 per cent below the peak rate recorded 2 years before. Even at this new level, however, the death rate from diabetes was appreciably above the level prevailing before the War. Since 1924, there has been no important interruption in the upward trend in diabetes mortality.

The rise in diabetes mortality in this country is also evident in the official statistics which are portrayed in Chart II. The reader is reminded that mortality data for the entire country or for the major part of it are available for a comparatively short period. The chart shows the death rates in the expanding Registration

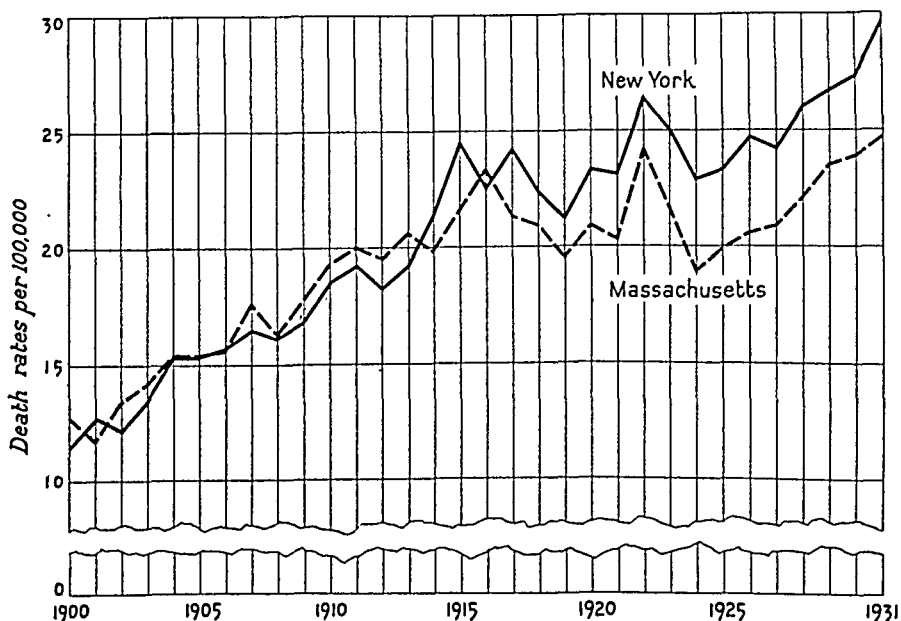


CHART III.—Diabetes death rates in Massachusetts and New York, 1900–1931.

Area from 1900 to 1931 and in the constant area comprised in the so-called Original Registration States from 1900 on. For reference we have inserted in the chart the death rates for the census years 1880 and 1890 for the small Registration Area in those years for which the data are available. The death rates in these series do not take into account changes in the sex, color and age composition of the population. A third series has been added, therefore, which allows for these changes. This third series is limited to the period since 1910 and consists of the expanding Registration Area from 1910 to 1919 and of the Registration States of 1920 since the latter year.

The course of the diabetes death rates in the several areas is roughly similar and since 1910 they show no features that are essentially different from the experience already shown for Industrial

policyholders of the Metropolitan Life Insurance Company. The rise is most moderate in the case of the adjusted rates, but this is to be expected. The chief new feature of this chart is the story of diabetes prior to 1910. It shows that the broad advance in diabetes mortality since 1910 was no new thing, but had been going on for some time. Between 1900 and 1910, the diabetes death rate had increased by 50 per cent. Another striking fact is that 40 or 50 years ago, diabetes was relatively uncommon. The death rate was only 5.5 in 1890, or little more than a quarter of what it is now. Fifty years ago, the death rate was even lower—less than 3—or only one-seventh of the current death rate from the disease.

Next let us examine the long-term changes in diabetes death rates in local areas. For this purpose we have chosen Massachusetts and New York because in these two states the mortality records go back for many years and also because in them the quality of medical certification is about the best in this country. The first thing which attracts attention is the high level which the rates in these two states have reached. The trend of mortality in these states, however, is little different from that of the rest of the country. Since 1920 it is true that in Massachusetts particularly, the rise has been more moderate than in the other areas. Apart from this difference it is certain that even in these two states in which, if anywhere, we might expect some amelioration of the rise in diabetes mortality, because of their well developed medical services, there is none.

In Canada, available mortality records go back only to 1921. There, too, recent rates for diabetes are higher than a decade ago. In Canada, however, the rise has been more moderate than in this country.

In European countries, too, the diabetes death rate shows an upward tendency. In some of them they have increased even more rapidly than in the United States. In England, for example, the death rates in recent years have been the highest on record. That of 1931, 14.5, was 29.5 per cent higher than in 1925 and 45.0 per cent higher than in 1920. In Denmark, the 1931 rate, 15.9, was 20.5 per cent higher than in 1925 and 27.2 per cent higher than in 1920. Similarly, the 1931 rate for the Netherlands, 17.7, shows an increase of 22.0 per cent in 6 years and 40.5 per cent in 11 years. Italy's rate for 1930 was nearly double the rate for 1920. Generally speaking, the rising trend in diabetes mortality shows the same broad advance as that found in this country. Abroad also, the rising trend was marked by two brief interruptions: the first during the period of years just preceding and just following the World War; the second time, subsequent to the introduction of insulin.

National data for Germany and France are not available, but the data for the capital cities of both countries and of the German provinces conform to the general picture we have drawn.

The best data for other regions of the world relate to European

settlements, particularly the English colonies. In Australia, the trend of diabetes mortality has been upward and the 1932 death rate is the highest on record. The same is true in New Zealand and in the European population of South Africa.

In Japan, the only Oriental country with substantial data, although the death rates are low and possibly not reliable, there has also been a definite rise in diabetes death rates.

It would be interesting to know the trend of diabetes in the tropical areas and in the countries of South America, but the data are too fragmentary and unreliable to give us a clear picture of the situation in them.

Table 3 portrays the changing situation in the several areas for which the data have been collected.

TABLE 3.—DIABETES DEATH RATES PER 100,000 IN PRINCIPAL COUNTRIES OF THE WORLD, 1900 to 1931.

	1931.	1930.	1929.	1928.	1927.	1926.	1925.	1924.	1923.	1922.	1921.	1920.	1918.	1915.	1910.	1905.	1900.
United States†	25.6	24.0	24.1	23.6	22.0	22.0	21.0	20.3	22.1	23.2	20.7	20.4	20.2	21.5	17.6	13.9	11.0
England and Wales	14.5	14.2	14.2	13.1	12.6	11.5	11.2	10.9	11.4	11.9	10.8	10.0*	10.3*	13.0*	11.0	9.3	8.6
Sweden	17.7	17.6	17.8	16.3	16.3	15.9	14.5	14.2	15.0	14.0	12.7	12.6	10.7	13.1	9.9
Netherlands	8.2	8.1	7.4	7.1	6.3	5.9	5.8	5.4	5.4	4.9	4.5	4.8	5.3	4.7	4.0	3.3
Italy	8.7	8.2	7.6	7.6	6.5	5.8	5.0	5.6	5.2	6.3	7.7
Bavaria	9.4	9.3	9.3	8.5	8.3	8.2	7.9	7.3	7.3	6.8
Spain
Australia	13.9	11.2	12.9	12.0	13.1	11.3	11.4	11.6	12.2	12.3	11.5	11.5*	11.6*	10.4*	9.5
New Zealand	3.5	3.7	3.5	3.5	3.4	3.3	3.3	3.2	3.3	3.3	3.1	3.5	2.9	-1.8
Japan	12.0	11.2	12.0	11.1	11.1	10.9	9.3	9.5	10.9	10.8	9.5
Canada‡	8.1	6.3	5.4	5.1	5.3	5.1
Czechoslovakia	15.7	15.7	14.3	12.0	13.7	12.0	12.2	13.3	14.2	12.7	13.5	12.5	17.7	13.5	12.4	7.5
Northern Ireland	9.6	9.7	9.2	10.0	9.6	10.2	8.3	7.9	12.7	11.1	9.5	9.5	8.4	10.8
Norway	10.8	11.1	10.2	10.5	9.7	9.7	8.4	10.8	10.3	10.1	9.6	7.9
Scotland	13.6	12.5	12.7	10.8	10.7	10.7	9.4	10.0	10.6	10.8	10.2	9.0	9.1	11.4	9.7	7.2
Switzerland	10.4	11.0	10.7	10.3	10.3	9.1	9.2	8.9	8.6	8.7	7.8	7.7	6.4	7.6	5.6
Cuba	5.1	4.1	3.7	3.8	4.1	3.8	3.3	2.6
Denmark	15.9	14.5	13.2	13.4	13.0	13.1	13.2	12.5	14.2	15.1	14.5	12.5
Union of South Africa	15.7	13.6	13.5	13.0	11.7	11.6	10.6	12.4	9.0
Prussia	15.3	13.9	13.2	11.6
Irish Free State	8.2	8.0	7.8	7.9	7.8	7.6	7.4	7.1	7.4	7.9	6.9	7.6	6.8	8.9

* Death rates based on civilian population.

† Original Registration States.

‡ Expanding Registration Area.

It is clear from all these sources that few countries or localities have escaped the rising tide of diabetes mortality. The disease has continued to exact a mounting toll of human life although present knowledge would seem sufficient not only to save the lives of diabetics but also largely to prevent the disease. The causes of this rising trend are many and some of them are known, but before we look into them it would be well to review certain aspects of the mortality from the disease, particularly its sex and age characteristics, its racial and social aspects.

The Characteristics of Diabetes Mortality by Age, Sex and Color. Age. Diabetes is primarily a disease of later life. In early childhood and adolescence, the disease is relatively rare and the death-rates are low—about 2 in recent years, 1926 to 1930, among insured persons under 15 years of age and 3 in the succeeding decade of life. It is significant that there is a slight maximum at ages 15 to 19,

which covers the period of adolescence. This noticeable peak is probably indicative of the rôle of abnormal development in the causation of diabetes among young people at this stage of life. The mortality rises gradually through early adult life, as Chart IV shows, but after age 35 it increases rapidly. Compared with the preceding 10-year-age period, the death rate at ages 35 to 44 increases approximately two-fold; at 45 to 54, four-fold; at 55 to 64, over three-fold; and at 65 to 74, nearly two-fold again. The maximum

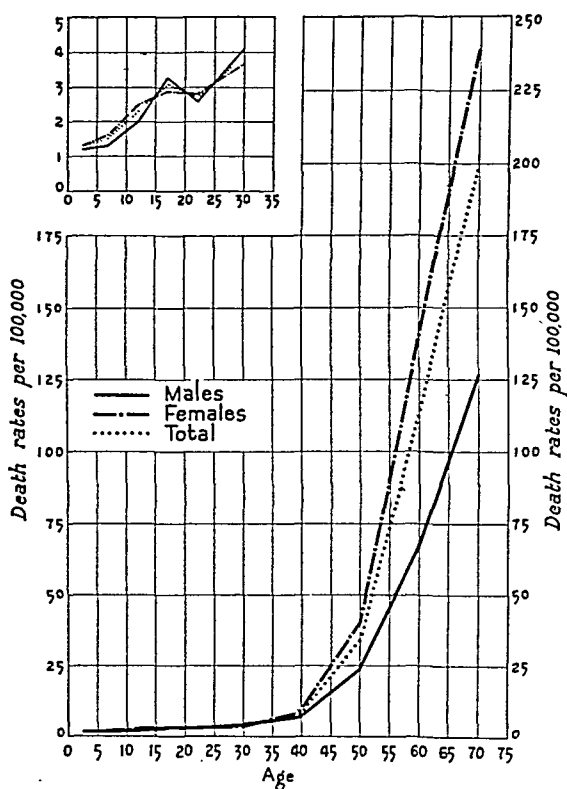


CHART IV.—Diabetes death rates by sex and age among white persons. Metropolitan Life Insurance Company, Industrial Department, 1926-1930.

death rate is reached in old age, but it is, then, not much or consistently higher than at ages 65 to 74.

The age curve of diabetes mortality in the United States is a characteristic one. The contours of the death rates by age in other countries are similar although, as would be expected, there are differences in detail. We shall not go into these differences at this point.

Sex. The mortality from diabetes among women is now much higher than among men, contrary to the early clinical experiences which showed a predominance of male patients. At all ages 1 to 74,

the death rate for females in the 5 years ending in 1930 exceeded that for males by 75.9 per cent. It is clear from Chart IV that the whole excess of diabetes in females is limited to middle life and old age. In childhood and early adult life, the rates of the two sexes differ little. Around menopause, the female rate begins to increase very rapidly, much more so than the rate for males of corresponding ages. This high rate of increase continues for the next 30 years of life, and as a result the rates for women exceed those for men by an increasing margin with advancing age. Thus, at ages 35 to 44 the excess of the female rate over that for males is only 28.8 per cent, but increases rapidly to 68.9 per cent at ages 45 to 54, and reaches a maximum of 108.4 per cent at ages 55 to 64. The excess is smaller in later life. At ages 65 to 74 it amounts to 89.0 per cent.

This excess mortality from diabetes of women, as compared with men, is characteristic of the diabetes situation today. It is found in other countries beside the United States, although the actual excess differs appreciably from country to country. Thus, in England and Wales the diabetes death rate of females at all ages is but little more than 10 per cent higher than the male rate. Up to age 35, female rates are somewhat lower than those for males, and it is only after age 45 that there is any appreciable excess in the female rates. The maximum difference in the rates of the two sexes is only one-third, and occurs between ages 55 and 64.

In New Zealand, the diabetes death rate of females is more than 50 per cent higher than that of males. In that country the rate for women is consistently higher throughout adult life, and the differences in the mortality of the two sexes are as large as in the United States, reaching a maximum at ages 65 to 74, when the rate for women is more than double that for men. In Denmark, the female death rate from diabetes is about one-fourth higher than the rate for males. In that country, however, there is little difference in the level of the mortality of the two sexes until late middle life. After age 55, the rate for women is appreciably higher than that for men, the excess increasing with advancing age. In the Netherlands, the difference in mortality between the two sexes is most marked: present rates for females are nearly double those for males. In Australia, too, the female rate is greatly in excess of that for males in the last 5 years. In the 5-year period ending in 1930, the female rate averaged about two-thirds in excess of the male rate. Unfortunately, the age specific data for the last two countries are not available and we cannot tell whether or not the differences in the mortality of the two sexes are limited to later life as in other countries.

In Table 4 are shown the death rates by sex in the years 1926 to 1930 in the several countries and by age also where these data are available.

TABLE 4.—SEX AND AGE CHARACTERISTICS OF DIABETES MORTALITY IN SEVERAL COUNTRIES.

Death Rates Per 100,000 in United States, England and Wales, New Zealand, Denmark, Australia and Netherlands, 1926 to 1930.

Age period.	United States.		England and Wales.		New Zealand.		Denmark.		Australia.†		Netherlands.†	
	Males.†	Fe-males.†	Males.	Fe-males.	Males.	Fe-males.	Males.	Fe-males.	Males.	Fe-males.	Males.	Fe-males.
All ages .	13.5*	20.3*	9.1*	10.2*	10.6	16.4	11.8	15.0	9.1	15.2	12.2	21.4
0-14 .	2.3*	2.5*	1.2	1.1	2.3	1.6	2.2	2.0				
15-24 .			2.7	2.3				2.9				
25-34 .	3.5	3.6	3.7	3.2	2.6	3.7						
35-44 .	5.8	7.6	4.6	4.7	2.7	4.5						
45-54 .	17.3	28.8	9.4	11.9	11.1	20.5	13.1	12.7				
55-64 .	57.0	102.0	33.0	44.5	28.5	51.4	42.6	52.7				
65-74 .	118.6	189.1	82.5	95.9	78.0	159.1	80.2	101.0				
75 and over .	158.8	190.5	108.2	107.6	158.2	190.4	83.8	107.0				

* Standardized.

† White only.

‡ Age data not available.

Sex and Age Characteristics in the United States and in Other Countries Compared. It will be interesting next to compare the diabetes mortality by sex and age in this country with that in other lands. Further examination of Table 4 from this point of view shows that the death rates for both males and females in this country are higher than in any other for which this record is available. At the younger ages, in both sexes, the diabetes death rates in all countries are very much alike. Beginning with age 35 the death rates in this country forge ahead, and by age 45 there is a considerable margin between the diabetes death rates in this and other countries. All through the rest of the life span the diabetes death rates of this country are higher than those abroad. Only at ages 75 and over do we find the rate in one country, namely, New Zealand, on a par with that in this country. These statements apply both to males and females.

Sex and Age Characteristics Among Negroes. The large number of negroes in our population demands consideration of the facts on the diabetes mortality of that race in this country. For them, the data on insured persons are most instructive. While these relate to all colored policyholders, the group consists almost entirely of negroes.

During the early years of this mortality experience, it was thought that the negroes were relatively immune to diabetes. The death rate of colored persons 20 years ago was only two-thirds that of whites. The error in this earlier view has become increasingly evident. In the 5-year period ending in 1930, the mortality of colored persons has been but little lower than that of the white race. This statement is true for both sexes.

The diabetes mortality of negroes is marked by relatively higher rates in early adult and middle life. Thus, in the period 1926-1930, the rate of colored men at ages 25 to 34 exceeded that of whites

by 17.1 per cent; at ages 35 to 44, by 27.3 per cent; and at ages 45 to 54, by 15.7 per cent. Among females, the differences were even greater. At ages 25 to 34, negro rates exceeded the white by 81.1 per cent; at ages 35 to 44, by 163.5 per cent; and at ages 45 to 54, by 61 per cent. In old age, rates of colored persons of both sexes were much below those for whites, and in early life, approximately the same as the rates for white persons.

As among whites, there is a characteristic rise of diabetes mortality with age among colored persons. Similarly, the rates of colored women are higher than those for men. This difference is greatest between ages 35 and 44, and declines thereafter. Among whites, on the other hand, the maximum difference in the mortality of the two sexes is not reached until 20 years later, *i. e.*, between ages 55 and 64.

Table 5 gives the rates for colored policyholders of the Metropolitan Life Insurance Company.

TABLE 5.—SEX AND AGE CHARACTERISTICS OF DIABETES MORTALITY OF COLORED PERSONS.
Death Rates Per 100,000 Among Colored Policyholders, Metropolitan Life Insurance Company, Industrial Department, 1926 to 1930.

Age groups.	Males.	Females.
Ages 1 to 74 years*	11.9	23.2
1 to 4	3.2	1.4
5 to 9	0.6	1.3
10 to 14	1.8	3.2
15 to 19	2.9	2.4
20 to 24	2.6	3.3
25 to 34	4.8	6.7
35 to 44	8.4	22.4
45 to 54	27.2	63.9
55 to 64	54.3	114.1
65 to 74	86.7	144.0

* Standardized.

Trends in Diabetes Mortality by Sex—United States. The next step in our analysis is to determine whether there are any differences in the mortality trends by sex. We have already seen that for the population as a whole there has been a broad advance in diabetes mortality for a long period of time. Examination of the rates for males and females separately showed distinct differences. Again, using the carefully recorded data on persons insured by the Metropolitan Life Insurance Company, we find that for white males the diabetes standardized rate at all ages 1 to 74 has been remarkably stable for two decades. The minimum rate of 12.3 was registered in 1924; the maximum of 14.5 registered in 2 years, 1923 and 1916. The tendency of the trend for white males has been downward, but the actual decline, by the usual statistical tests, is not really significant. Among colored males, the trend has been upward. Their death rate is much closer to that of white men today, although in the earlier years of this study, it averaged about one-third less.

In contrast to these moderate changes among males are the very

sharp and unmistakable increases in the rates of women, both white and colored. Among white women, the increase has averaged annually 1.5 per cent of the mean rate of the two decades. The course of the rate among insured white women is in its details similar to that of the total insured population, which we have already described, differing only in that the upward swings are more accentuated.

Negro women have experienced an even sharper rise in diabetes mortality than white women. Their death rate in the early years of the insurance experience was barely half that of the whites. Within the short space of 20 years, however, the picture has changed completely. Increasing at a rate which has averaged 5.4 per cent per annum of the mean rate of the last two decades, the mortality of colored females has caught up with that of white females, and in some recent years has actually exceeded it.

Other Countries. The relatively stable death rate from diabetes among males and the rapidly rising mortality among females which we found in the United States appears to be characteristic of the trends in the disease everywhere. In England, for example, the long-term trend of death rates, adjusted for age, among males has been downward, although for the last 5 years it has shown a tendency to increase. Nevertheless, the rate of males in England in recent years has been substantially below that prevailing 20 years ago. Among females, on the other hand, recent rates have been the highest recorded, and this rise has been going on with little interruption over the last 10 years. It is of interest to note that only since 1923 have the diabetes death rates of women in England been higher than the male rates.

In the Netherlands, the rate of males has been rising, but at a much slower pace than that of women. Thus, the diabetes mortality of men has risen about one-third in the last 20 years, and about one-fifth in the last decade. This is in sharp contrast to the increase of 75 per cent in the female rate in the last 20 years, and of 50 per cent in the last 10.

In Denmark, Australia and New Zealand, similar changes have occurred. In all these countries the death rates from year to year show large fluctuations because of the relatively small populations, but in the case of men they show a clear-cut tendency to rise moderately during the last few years. Present rates for men, however, are appreciably below the maxima reached 10 years ago. Among women, on the other hand, there has been a sharp rise in mortality from the disease in these countries, with the maximum rates recorded in very recent years. The detailed data on these changes are shown in Table 6.

Age and Sex Trends in Diabetes Mortality. The larger movements in the death rates from diabetes at all ages, both for men and women, conceal significant and contrary trends at the different periods of life. Stated most briefly, among white persons the rise in diabetes mortality has been limited to older persons; among men,

TABLE 6.—TRENDS OF DIABETES MORTALITY OF MALES AND FEMALES IN SEVERAL COUNTRIES.

Death rates per 100,000.						
Year.	United States.*†	England and Wales.*	Australia.	New Zealand.	Netherlands.	Denmark.
<i>Males:</i>						
1931	9.7	12.3	12.0	
1930	13.5	9.3	8.7	10.9	12.1	
1929	13.8	9.5	10.1	10.0	12.8	
1928	14.0	9.1	9.0	10.7	11.6	11.8
1927	12.8	8.8	9.4	11.8	12.4	
1926	13.5	8.6	8.4	9.8	12.0	
1925	12.9	8.1	9.0	8.4	10.2	
1924	12.6	8.6	9.5	8.8	10.8	
1923	14.6	9.0	9.9	12.6	12.0	13.4
1922	15.4	10.1	10.0	9.9	11.3	
1921	14.0	9.2	9.4	10.9	10.4	
1920	14.0	8.9	10.9	10.7	
1919	12.6	10.0	10.8	11.5	
1918	13.8	12.2	9.5	10.1	
1917	14.7	12.5	9.3	10.2	
1916	14.4	14.1	9.7	12.0	
1915	12.2	13.5	9.7	11.6	
1914	14.4	12.4	7.9	11.5	
1913	13.6	11.7	9.5	9.7	
1912	13.5	11.5	7.4	9.5	
1911	13.7	10.8	7.5	9.3	
1910	13.6	7.9	8.8	
<i>Females:</i>						
1931	18.2	18.7	23.3	
1930	20.8	10.8	13.8	20.2	23.1	
1929	20.8	11.1	15.9	18.7	22.8	
1928	21.2	10.1	15.1	13.4	21.0	15.0
1927	19.2	10.1	17.0	15.6	20.1	
1926	19.5	9.1	14.3	14.2	19.8	
1925	18.3	9.4	13.9	16.1	18.8	
1924	18.0	8.9	13.7	18.1	17.5	
1923	19.1	9.4	14.5	15.8	17.8	14.3
1922	20.1	9.7	14.7	15.7	16.7	
1921	18.2	8.9	13.7	16.2	15.0	
1920	17.3	8.6	12.1	14.6	
1919	15.6	8.6	13.7	13.6	
1918	16.3	7.9	13.6	11.2	
1917	17.4	8.5	12.9	15.1	
1916	17.9	10.2	11.1	15.1	
1915	19.2	10.7	11.1	14.5	
1914	17.4	10.6	11.1	13.1	
1913	16.2	10.3	10.8	13.4	
1912	15.7	9.4	11.5	12.6	
1911	15.4	9.2	11.0	13.2	
1910	15.7	11.2		

* Standardized.

† Registration States of 1920 in 1920 to 1931 and Expanding Registration Area 1910 to 1919. White persons only, 1920 to 1931.

to those over 60; among women, to those over 50. Among children and young adults, however, there has been definite and substantial improvement in the diabetes death rate. This phenomenon is not limited to the United States, but is found in other countries for which we have data. It will be of interest to see the extent of these changes in the several populations, and we shall first concern ourselves with the experience on insured lives. This is given in detail in Chart V.

Improvement in Diabetes Mortality Among Children. The first striking feature of this insurance experience is the large decline in the diabetes mortality of young persons. This is most interesting and significant, because it seems to be a direct result of improvement

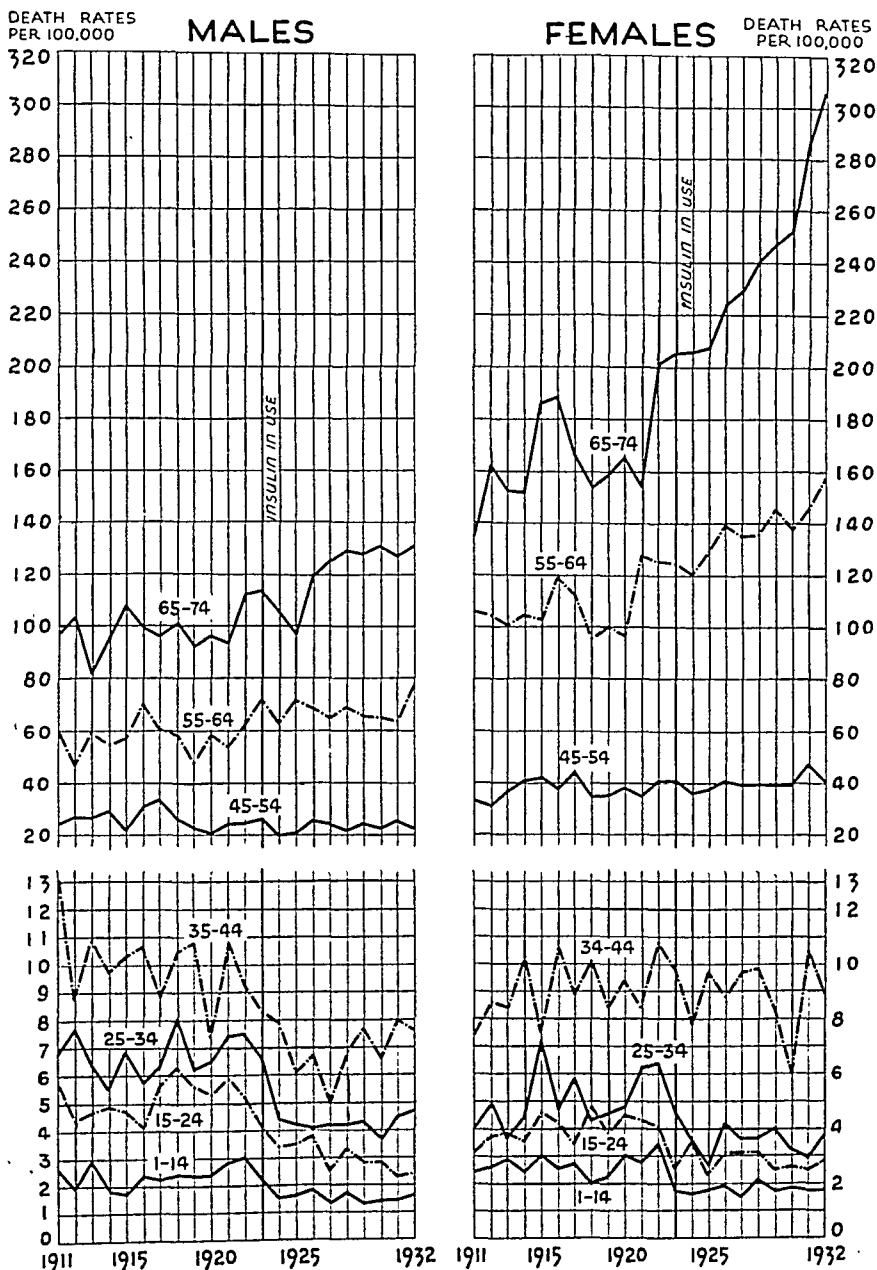


CHART V.—Sex and age trends in diabetes among white persons, Metropolitan Life Insurance Company, Industrial Department, 1911–1932.

in the treatment of diabetes by the use of insulin. Prior to its discovery the trend of diabetes was upward among children and young people. Following immediately upon the inauguration of insulin treatment, the death rate among white males at ages under 25 dropped from 4.0 in 1922, to 3.0 in 1923, and among white females, from 3.7 to 2.0. Subsequently the death rate has fallen still further among young males, and in several years has been under 2.0. Among young females, the death rate has dropped below this figure only once, but it has remained distinctly below the pre-insulin level.

Over the long term the extent of this change among young people is very large. In the 8-year period, 1923-1930, the mean rate of males under 25 was only 2.3—a decrease of 34.3 per cent from the average rate of 3.5 which prevailed in the 12 years preceding the introduction of insulin. Among young females, the drop was little less, amounting to 31.3 per cent for the same period.

Diabetes Mortality in Early Adult Life. Here also, there has been marked improvement in the mortality from diabetes, particularly since the discovery of insulin. Prior to 1922, the death rate among white men between the ages of 25 and 44 had fluctuated with a slightly downward tendency around a mean of 8.2. From this level it has fallen considerably in the years 1924 to 1930 to only 5.2 among these insured men, or 36.6 below the level prevailing in the 12-year period ending in 1922. Although there has been a slight upward tendency in their mortality in very recent years, the present death rates of men at these ages are still far below those prevailing a decade ago.

Among white women, the improvement in the death rate at ages 25 to 44 is less than among men. In the period from 1924 to 1930, the mean rate at these ages was 5.7, a drop of 16.2 per cent from the level prevailing in the period 1911 to 1922. This improvement is less than half that of males at these ages. The tendency of the death rates among these younger women in the insulin period has, however, been downward and the rate of fall is about the same as that among men at the same ages.

Diabetes in Middle Life and Old Age. Among persons in middle life there has been little if any rise in the death rate of men, but a distinct rise among women. In old age, however, there has been a very sharp advance in the mortality for both sexes, but here, too, women have suffered more than men. Taking the age group 45 to 74 as a whole, the mortality of white men in our insured group has risen in the two decades ending in 1930 at a rate of 0.43 deaths per annum, and of white women, 1.85. Compared with the average diabetes death rate for the whole period, these figures correspond to an annual increase of 0.8 per cent for men and 2.0 per cent for women.

These differences in the rates of change of the diabetes death rate between the various sex and age groups have resulted in extremely interesting changes in the relative mortality of males, as compared

with females. Among these insured persons the mortality of males at ages under 45 was formerly 15 per cent in excess of that of females, but in the insulin period the male rate has been slightly the lower of the two. At ages over 45, the excess of the female diabetes death rate over that of males has risen from 70 per cent in the period 1911-1922, to 90 per cent in the years 1923-1930. If we consider the changes in smaller age groups, we find that at ages 45 to 54 the excess of the female rate in recent years has been 70 per cent, whereas formerly it was but 40 per cent; at ages 55 to 64 nearly 100 per cent, as compared with less than 90 per cent formerly; and at ages 65 to 74, 90 per cent, as compared with only 70 per cent in the earlier years.

Sex and Age Trends Among Colored Persons. The trends in the diabetes mortality of colored persons by sex and age resemble, in some ways, the changes that have taken place among white persons. Thus, the death rates of colored men and women in old age show very striking increases. In the age group 45 to 74, the rate of colored men has increased by 0.56 deaths per year in the two decades ending in 1930, and among colored females by 3.50 deaths in the same period. The rate of increase has been 1.4 per cent per annum among the colored men and 5.5 per cent among colored women at these ages. These rates of increase are far higher than those recorded for white persons.

There is a distinct difference between the two races in the trends of diabetes mortality in childhood and early adult life. In contrast to the improvement in young white persons of both sexes, there has actually been an increase in the mortality of young negroes.

Sex and Age Trends in the United States and Foreign Countries Compared. We have observed that the essential features of change in diabetes mortality are characteristic not only of the mortality in the general population of this country, but of foreign countries as well. There are, of course, differences in detail in the situation in the various countries of the world. For example, the rates of change in the death rates in the specific sex and age groups are not the same everywhere. Again, among insured wage earners in this country, the mortality from diabetes is rising in women past 50, and in men past 60, but in the general population of this and other countries, the initial age at which this rise begins differs by a few years at least, in various places. Apart from these minor differences, however, the picture is everywhere very much the same.

To show this situation in all its detail would require considerable space. It will suffice, however, to give a few examples which will illustrate this clearly. In Table 7, we show changes in the death rate by sex and age in the period 1926 to 1930, as compared with the 3 pre-insulin years, 1920 to 1922* for several areas.

Let us first review the situation among males. The table shows

* In Denmark and New Zealand, comparison is made between 1926-1930 and 1921-1925.

that in none of the areas surveyed are the diabetes death rates in 1926 to 1930 higher than the rates in pre-insulin years until late middle life is reached, and in some countries this improvement extends well into old age. In the general population of this country and in England and Wales, the diabetes death rates in 1926 to 1930 are lower at every age up to 55 than in 1920 to 1922, and in Scotland, Denmark and New Zealand lower at every age up to 65. The extent of this decline at some ages is very large indeed, reaching beyond or approaching 40 per cent in several of the areas. An increase in the diabetes mortality of men is first noted in the age group 55 to 64 in the general population of this country and in England and Wales. The rise at these ages is, however, very moderate. Past age 65, the increases are quite large and are particularly significant, because the diabetes death rates reach their maximum at these ages. In Denmark and New Zealand there has been only a moderate rise in the death rate of men between 65 and 74 during the last decade, but a very distinct one after age 75.

TABLE 7.—TRENDS IN DIABETES MORTALITY IN THE UNITED STATES AND CERTAIN FOREIGN COUNTRIES.

(Percentage Change in the Death Rates Between 1920-1922 and 1926-1930).

Age and sex.	Per cent increase (+) or decrease (-) between 1926-1930 and 1920-1922.					
	Metropol. Life Ins. Co. Industrial Dep't.	United States.†	England and Wales	Scotland.	Denmark.*	New Zealand.*
Males:						
Under 15	} -46.2‡	} -45.2‡	-14.3	-33.3	-29.0	} -20.7
15-24			-35.7	-28.9		
25-34	-42.3	-48.5	-38.3	-57.7	} -55.6	-27.8
35-44	-27.5	-34.1	-33.3	-38.7		-34.1
45-54	+ 2.2	-11.3	-29.3	-24.8	-19.6	- 8.3
55-64	+14.8	+ 4.2	+ 6.8	-13.7	- 9.6	-18.8
65-74	+25.5	+19.2	+24.8	+17.7	+ 4.8	+11.1
75 and over	**	+20.5	+40.0	+32.7	+26.8	+68.7
Females:						
Under 15	} -37.1‡	} -34.2‡	-31.3	-50.0	-47.4	} -36.0
15-24			-34.3	-35.1		
25-34	-36.2	-35.7	-33.3	-27.1	} -44.2	+32.1
35-44	-10.5	-10.6	-24.2	+ 9.4		-39.2
45-54	+ 4.5	- 1.7	- 4.0	+21.6	-21.1	+ 3.0
55-64	+19.2	+15.1	+25.4	+22.3	+22.6	- 7.6
65-74	+37.5	+31.1	+46.2	+36.6	+20.5	+ 1.5
75 and over	**	+33.1	+70.3	+73.3	+40.8	-19.2

* Between 1926-1930 and 1921-1925.

† U. S. Registration States of 1920.

‡ Standardized.

** Rates not significant because of small population.

The table also shows that in the case of females in most countries the diabetes death rates in more recent years are lower than in pre-insulin years at every age up to 50. Among females in this country

and in England, there has been measurable improvement in the rates up to age 45, and a slight fall between ages 45 and 54. In Denmark, substantial improvement is found at all ages up to 55. In Scotland, however, there is already an appreciable increase in the rate in the broad age group 35 to 54. After age 55 recent death rates are distinctly higher than a decade ago in every country surveyed with the exception of New Zealand. In practically every instance, the later the age, the greater has been the increase in the mortality from diabetes. The most striking increases are those of over 70 per cent in England and Wales, and in Scotland among women past 75 years of age. In passing, attention may be called to the situation in New Zealand where there has been an increase in the rate among older males, but not among older females. In that country, however, the rates of females reached a high level much earlier than in most countries, and present rates of women are still much higher than among men.

This table also brings out in very striking fashion two essential features of the changing situation in diabetes; first, that the decreases in the rates of males extend over a larger part of life than is the case with females and, for the most part, are proportionately greater than the declines among females; and, secondly, that diabetes mortality not only begins to increase at an earlier age among females, but these increases are much larger than occur among males.

Summary. Analysis of available mortality data on diabetes in this country and abroad during the present century brings out these main features.

1. Diabetes as a cause of death has been rapidly growing in importance during the present century and is now one of the leading causes of death in this country.

2. The mortality from diabetes in this country is higher than in other parts of the world.

3. Diabetes death rates are increasing all over the world.

4. Most of the deaths from diabetes occur after middle life. Among children and young adults, the mortality from the disease is low. It begins to loom large about age 40 and the rise in the death rates by age thereafter is rapid.

5. Up to age 35 present death rates of males and females are little different, but after that age the rates of women are the higher. This excess of the female death rate increases with advancing age up to 65, when it is about twice that of males.

6. The high diabetes mortality in this country, as compared to other countries is not limited to one sex, but is found among both men and women. It is also found to exist at almost every age past 35.

7. The diabetes mortality among negroes in this country has been increasing at a more rapid rate than among whites, and is now not much lower than that of whites.

8. The diabetes mortality of negroes is distinguished by relatively higher death rates in early adult and middle life.

9. At all ages combined, the trends in diabetes death rates over the past two decades among males in this country and England have been slightly downward, although there has been a tendency in recent years for these rates to increase. In most other countries, there has been a moderate increase in the long-term trends of mortality from the disease. Among females, however, there has been a substantial rise in diabetes mortality, both in this country and abroad.

10. Analysis of death rates by age, however, shows that in childhood and in early adult life there has been distinct improvement both among males and females. In the case of men, this improvement extends right through middle life and into the early part of old age. Among women, improvement ceases by age 50 and there are substantial increases in the death rates during late middle life and throughout old age.

This analysis of the diabetes situation in this country and abroad clearly indicates that the problem of its increasing mortality is circumscribed. It is one of controlling the disease in older people, chiefly in women. The increase in diabetes is thrown into sharp relief because it is just these groups which are increasing most rapidly in our population. On the other hand, it is certain that there has been a substantial growth in the incidence of diabetes throughout the world. We are forced to this conclusion because the mortality from diabetes has been increasing in the face of unmistakable improvement in the treatment of the disease. In our next paper, we shall concern ourselves with this matter of the incidence of the disease and the various factors which, on the one hand, make for increasing mortality and also those which tend to moderate it.

NOTE ON THE PRESENCE OF GASTRIC ACIDITY IN MULTIPLE SCLEROSIS.

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MULTIPLE sclerosis remains a disease of unknown etiology despite extensive investigations along many lines. The literature recording these has been summed up by the Association for Research

in Nervous and Mental Disease.¹ No mention, however, is made of the findings by gastric analysis in this condition.

There are certain reasons why such data should be available. Not only is it needed for completeness of the study but also because of various analogies which exist between multiple sclerosis and the syndrome of Addisonian anemia, posterolateral sclerosis and gastric

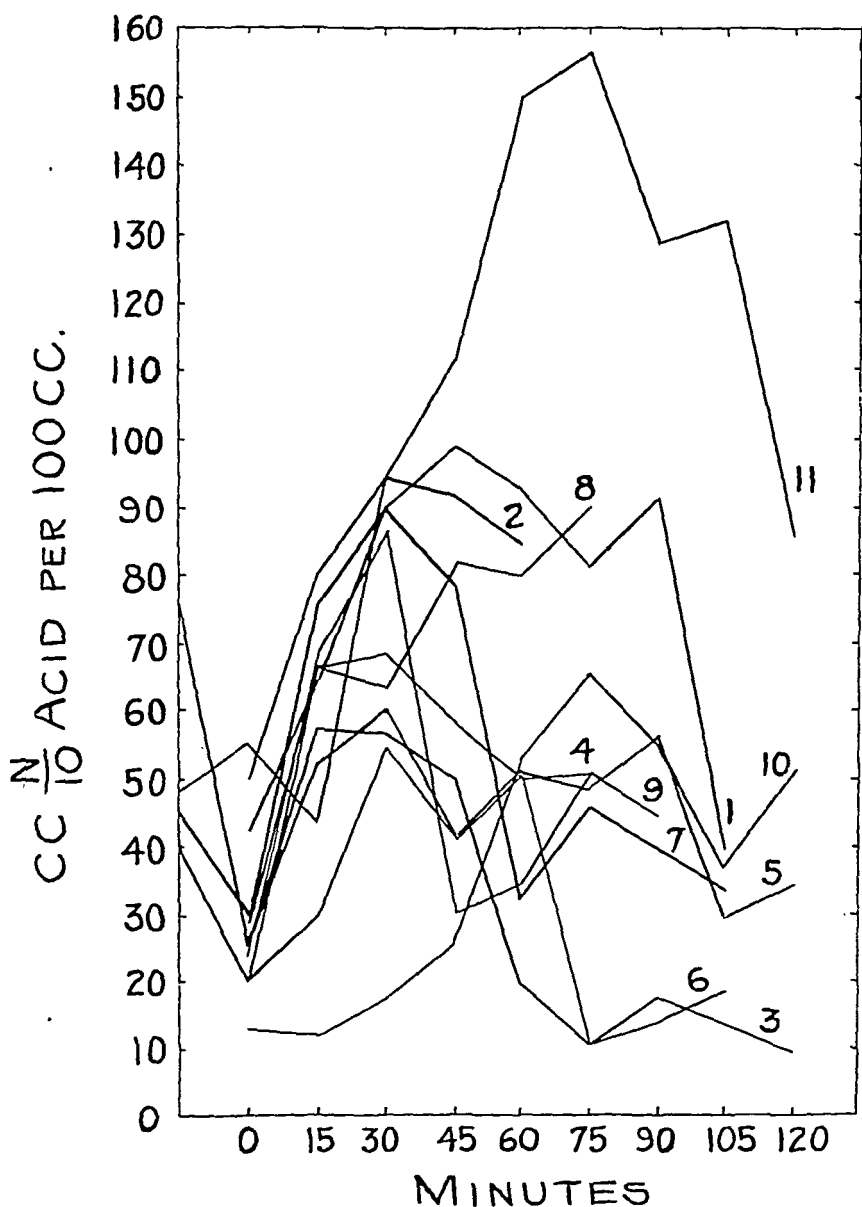


FIG. 1.—Total acidity of gastric contents in multiple sclerosis.

anacidity. These analogies do not need to be fully discussed here and it will suffice to point out the great frequency of remissions in both, the unknown etiology, the age and sex incidence, the occasional familial occurrence, and the occasional relationship to infection and to pregnancy.

In addition the nervous system involvement presents points of resemblance not only in the areas involved but also in the sclerotic nature of the process and to some extent in its vascular distribution.

Our attention was directed to this subject by the finding of anacidity in a patient with undoubted multiple sclerosis in whom no com-

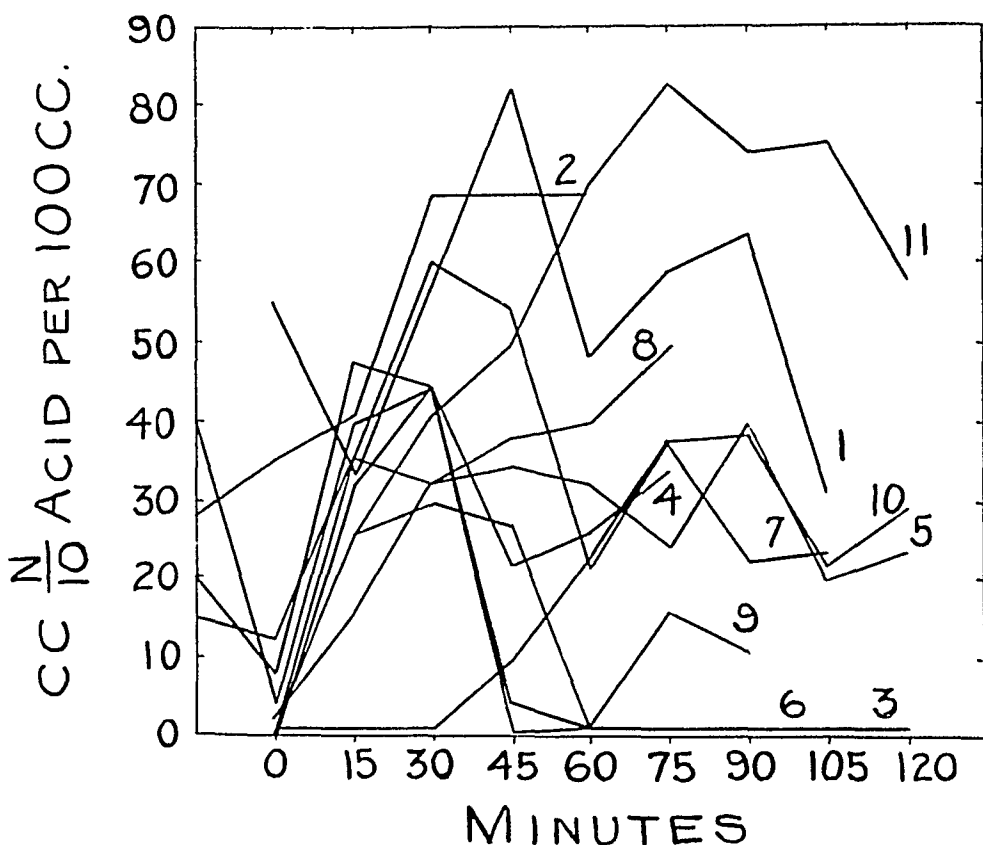


FIG. 2.—Free hydrochloric acid of gastric contents in multiple sclerosis.

plication likely to cause anacidity could be discovered. Of course such a finding in a single case is of little or no importance, as anacidity occurs in a great number of individuals not only in the presence of a variety of diseases, but even in persons apparently healthy. However, it seemed desirable to study this matter in a series of cases of multiple sclerosis and our findings are here reported in order to place these data on record.

The patients whose gastric acid curves are herewith recorded fulfill all of the requirements for a diagnosis of multiple sclerosis even of the most exacting diagnostician, and it is extremely doubtful

if fault could honestly be found with any of the cases from a classification standpoint. The usual Ewald meal was used.

Comment. It will be seen from an analysis of the curves, that free hydrochloric acid occurred in all cases, and in good amount. The original case which prompted the investigation was the only one in which free HCl was absent.

REFERENCE.

1. Multiple sclerosis (disseminated sclerosis) an investigation by the Association for Research in Nervous and Mental Diseases. Edited by C. L. Dana, S. E. Jelliffe and H. A. Riley, New York, P. B. Hoeber, Inc., 1922.

THE STRUCTURE AND FUNCTION OF FILAMENTS PRODUCED BY LIVING RED CORPUSCLES.¹

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PECULIAR filaments that converted normal, living red corpuscles into microcytes in hanging drop preparations were mentioned in a former paper;² in the present paper the origin, structure and function of these filaments will be described for the first time. This account gives the result of continuous observation of selected filaments, and the progression of changes was each directly seen in one filament-bearing red corpuscle.

Literature. These filaments are not described in the various reviews and a search of the literature yielded only the article of Kite.³ Kite studied the living blood cells and paid special attention to those of frog, rabbit and man. The blood was diluted with Ringer's solution containing hirudin, or citrate or oxalate was added. His slides were apparently the ordinary sealed coverslip type. Kite describes as many as 15 short, rapidly moving "processes" in one focal plane on a human erythrocyte, and remarks that "occasionally a long process is completely retracted in much less than a second" (p. 337); he does not mention any changes in form of the motile processes, nor does he record any deformation of red corpuscles produced by their activity.

¹Filament-like structures have been seen in sickle-cell anemia.⁴ In this complex, many of the red corpuscles are crescentic or sickle-shaped and such cells were first observed by Herrick.⁵ Emmel⁶ and others saw "long, tapering, hairlike processes" of "elliptical, spindle-shaped and sickle-shaped red corpuscles;" Diggs⁷ pictures some typical spindle-shaped red corpuscles with filament-like prolongations. Though none of the investigators describe any motility of these processes and though none have seen any causal relationship between them and the form of the corpuscle, yet it seems quite probable that the hairlike processes in sickle-cell anemia are identical with the filaments of normal blood described in this paper.

Structures that are possibly derived from the filaments described here have recently been reported by Edelmann⁸ who saw actively motile, round, oval or dumbbell-shaped bodies measuring 1 to 2 μ in diluted citrated or heparinized blood of normal and pathologic human cases. Their activity persisted at times for days and was strong enough to move red corpuscles. Edelmann is inclined to attribute an important rôle in coagulation to these "Kinetocytes."

Technique.² The living red blood corpuscles were studied in the periphery of broad-based hanging drops and occasionally in ordinary, sealed cover-slip preparations. Stained preparations were carefully avoided because the main object of this work was to see the filaments in action; furthermore it was felt that a study of the living, original text is always more wholesome than a study of the understatement, overstatement and interpolations of a dead translation. It may be remarked that the unbalanced routine of examining blood only as a seductively painted, coagulated corpse perhaps explains why many of the observations set down here were not seen before.

Blood was obtained from man, dog, rabbit, guinea pig and frog; the donors were apparently normal unless the opposite is stated. Coagulation was allowed to occur spontaneously, or was modified or prevented by $\frac{m}{8}$ sodium oxalate, hirudin or heparin.

The optical equipment has been described before;² in the present study a Zeiss cardioid condenser with the iris-objective X No. 60 was used for dark-field work. Several permanent light filters* were of service in bright-field work and various solutions were employed.

Most of the examinations were made with polarized light. In order to determine whether or not a structure was doubly refractile, the nicols were permanently crossed and the centered stage rotated through 360°. The gypsum plate R. I. was always used. The polarizing outfit was the Zeiss III set.

Observations. *The Filament.* After preparing a hanging drop, an examination of its thin peripheral border sooner or later shows an area where some, or many, or most of the red corpuscles have been distorted into a spindle (Fig. 1). This may occur within 2 minutes after obtaining the blood, and may continue to be observable for 24 hours and longer in different areas. Careful observation of these spindles shows round, tapering filaments extending from their apices. These filaments are moderately refractile, isotropic, homogeneous, clean-cut in outline and are thickest at their corpuscular origin; they look like colorless prolongations of the surface-layer of the red cell and their delicate distal end may be attached to another corpuscle, to a blood shadow (Fig. 50), to a platelet, to the edge of the drop or it may become invisible before any attachment is seen (Fig. 1). Their thickness near or at the corpuscle appears to be approximately 0.25 μ ; their visible length fluctuates between less than 5 μ and 75 μ ; if more than one filament issues from a corpuscle, then the length of each one is different. The number of filaments on a corpuscle varies from 1 to 5, but 2 are most frequent. The visibility of the filament differs at different times and disappearance and reappearance may be noted repeatedly in the

* For the stock filter-solutions, I am indebted to the kindness of Sister M. Aloyse Ellingson, Ph.D., who devised and made them.

same filament (Figs. 26, 27, 28). The filaments generally lie in a radial direction with reference to the blood drop, or at right angles to such a radius. When 2 filaments are present, these are usually located at opposite sides of the corpuscle (Fig. 1); if more than 2 are found, they too are often equally spaced along the circumference (Figs. 8, 9); regular spacing, however, is by no means invariable (Figs. 50, 51, 55). No filaments were ever seen arising definitely from the flattened surfaces of a corpuscle or microcyte; they were always attached to the rounded sides (Fig. 12). When multiple anchored filaments exerted traction upon a corpuscle, then their pull was usually in a plane parallel to the surface of the coverslip.

Filaments were seen issuing from round, oval, crumpled and crenated red corpuscles; from smooth microcytes and from microcytes

LEGENDS FIGS. 1 TO 25.

The accuracy of the measurements is roughly within 0.3μ ; no measurements could be made when the changes in the corpuscles or filament occurred swiftly. The number of beads sketched in a chain is arbitrary; they could be counted only under exceptional conditions as in Figs. 2 and 38 to 42; the connecting pieces between the beads are not drawn. The position of a cell in the different series has been occasionally altered in order to save space.

It should be observed that the different outline drawings in any one series sketch the consecutive changes seen in one and the same cell; the time interval between the drawings is recorded in the legend.

FIGS. 1, 2 and 3.—Human, ♂, X3-70; heparin-saline; hanging drop at 3.17 P.M.; the changes sketched occurred between 4.11 and 4.20.

FIGS. 4, 5 and 6.—Guinea pig, ♂, 620, X3-33; 10.04 A.M., blood from excised heart; 10.07, hanging drop, no dilution; 10.25, pear-shaped red, sways on filament (Fig. 4); reds do not stick to filament; passing red stretched filament strongly, rupture of filament and perfectly round red floated away with a glistening knob on periphery (Fig. 5); rolled over (Fig. 6); knob about 0.5μ .

FIGS. 7 to 11, inclusive.—Guinea pig, ♂, 610, X3-24; hemoglobin, 106 per cent (Dare). 1.25 P.M., hanging drop, no dilution. The changes sketched (Figs. 7 to 11) occurred between 1.29 and 1.30 P.M. For details see Reference 2, page 570, Groups D and E.

FIG. 12.—Guinea pig, ♂, 660, X3-37; hemoglobin, 100 per cent (Dare). 2.40 P.M., hanging drop, no dilution; 4.12, side view of red with a swaying, non-beaded filament, 26μ long (Fig. 12).

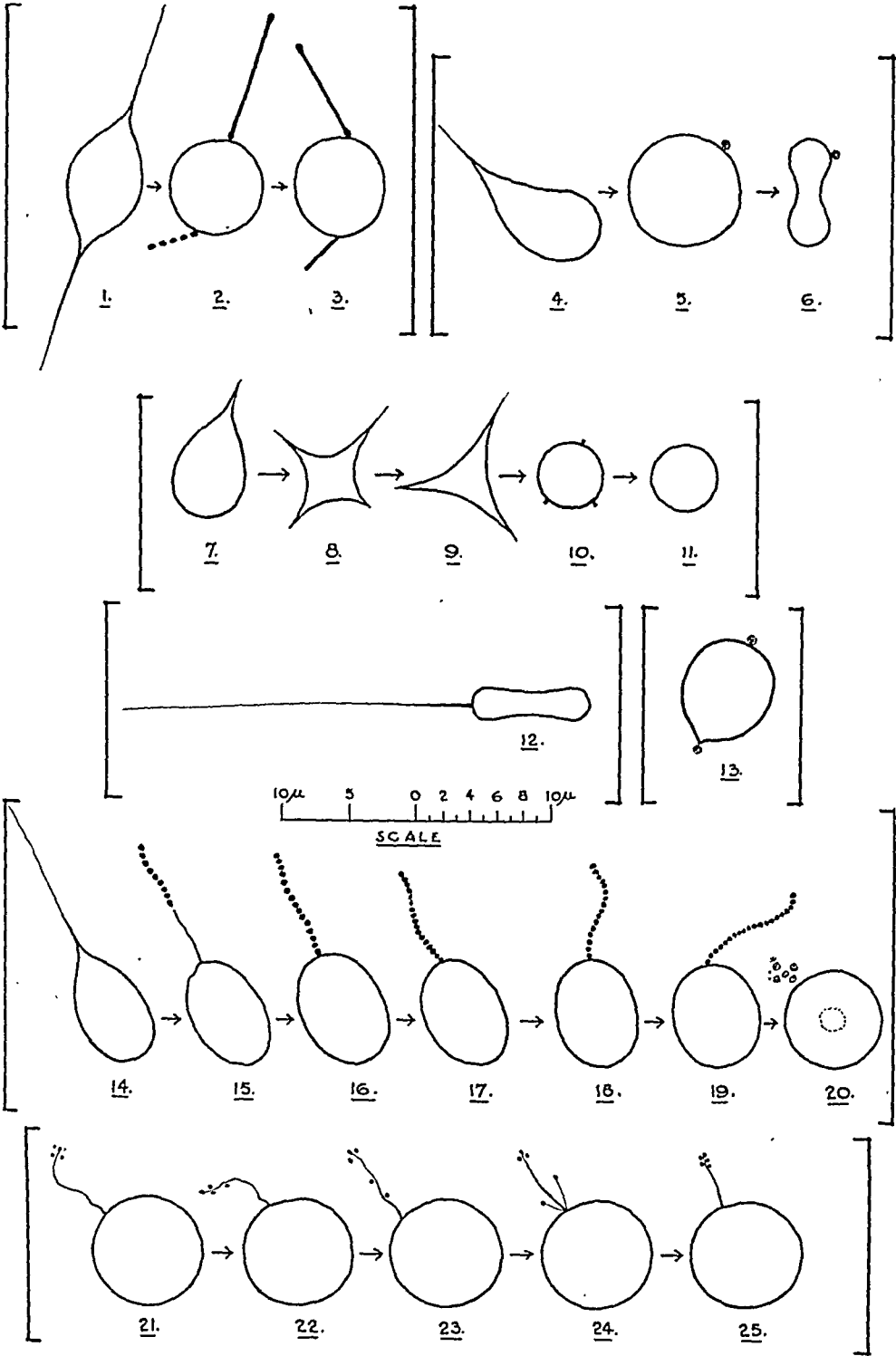
FIG. 13.—Human, ♂, X3-71; mixed with heparin-saline. 3.17 P.M., hanging drop; 5.05, red corpuscle with 2 refractile globules, lower one at apex of pointed pole (page 572, Group F).²

FIGS. 14 to 20, inclusive.—Gray rabbit, ♂, 2600, X2-50; hemoglobin, 93 per cent (Dare). 9.45 A.M., hanging drop, no dilution; 11.41, pear-shaped cell, no dells (Fig. 14); 11.43, filament became beaded part way (Fig. 15); 11.44, beading completed, more shortening; oscillates, quivers, hemoglobin normal (Fig. 16); 12.10, definite rotation of tip of chain to right, then left (Fig. 17); 12.50, no sign of dells; good hemoglobin; tip rotates rapidly right and then left; room temperature, 69°F . (Fig. 18); 2.10 to 2.25, no dells; hemoglobin same; rotation more active; occasionally a loop seems to travel from tip of chain to red corpuscle and then back (Fig. 19); 2.25 to 4.18 P.M., chain is very supple, loops travel to tip, then to corpuscle; 4.25, disintegrates into separate, slightly refractile rounded masses, motionless; globule liberated suddenly; shows a dells (Fig. 20).

FIGS. 21 to 25, inclusive.—Human, ♂, X3-68; hemoglobin, 90 per cent (estimated). 3.14 P.M., finger pricked through drop of saline; 3.15, spindle cells present. Transformations observed and sketched after 20 hours; occurred within 15 minutes; temperature, 72°F .

A similar untwisting of another filament was seen 26 minutes after preparing the hanging drop.

studded with delicate spicules; from blood shadows and from platelets. Fine filamentous projections were also occasionally seen on leukocytes, but these differed from the filaments of red corpuscles in refractivity, in motility and did not exhibit typical transforma-



Figs. 1 to 25.

tions. Leukocytes, however, were studied only incidentally when pseudopodal activity of especial beauty arrested the attention.

Dark-field illumination cannot be used with hanging drop preparations because an air space lies between the dark-field condenser and the slide, and therefore sealed, fresh blood films must be employed. Such film preparations were disappointing, for in 13 tests of normal human and guinea-pig blood, I only once obtained a fairly satisfactory slide with motile filaments. All these films were studied continuously for 3 to 4 tedious hours, both under bright-field and dark-field conditions; then they were reexamined 20 to 24 hours later for $\frac{1}{2}$ to 4 hours.

Activity and Mutations of the Filament. Interesting changes will be seen if selected corpuscles and their filaments are continuously observed. These filaments may at first be short and without visible peripheral fixation; gradually more of one or the other filament appears, or originally invisible filaments come into view and in association with these changes the corpuscular form is distorted. These alterations of form may occur abruptly or slowly and continuously (Figs. 7 to 11; 50 to 60). Associated with the changes in form, the filament near the corpuscle becomes thicker and less clear in outline. In this lower, slightly fuzzy section, transitory diagonal striations may be seen. These striations have an angle of less than 45° , run roughly from 8 to 2 o'clock or from 4 to 10 o'clock and resemble the thread of a right or a left screw. The striations appear and disappear, and the same filament may at one time show a right-handed and at another a left-handed striation. I was never able to decide whether or no the direction of striation was the same at any one time in the two filaments of a spindle. The filaments are remarkably elastic; they are stretched by passing corpuscles or by the lashings of filariæ, and then return to their former length. They may be stretched beyond their elastic limit and then one or both filaments tear. This rupture generally takes place in the periphery. If only one filament tears, then the spindle corpuscle changes into a pear-shaped structure which often darts across the field, apex in advance, toward the anchorage of its intact filament, while the torn filament rolls up instantaneously into a refractile, globular mass that comes to rest on the rounded edge of the corpuscle. The exact site of attachment of the globule was seen when a corpuscle rolled over; for example (Figs. 4, 5, 6) an originally pear-shaped corpuscle recoiled into a disk when the filament broke, and then turned on its side exhibiting the coiled filament as a ball perched at the junction of a concave surface with the rounded lateral side; in another example, a filament $26\ \mu$ long was attached to the middle of the lateral surface of a biconcave blood disk (Fig. 12). That the other, intact filament still exerts a pull is betrayed by the conical tip of the corpuscle where the filament arises; in addition this intact filament, which is rotating rapidly on its long axis, may

exhibit a series of open traveling loops that sway rapidly from side to side and occasionally a closed loop may run from the corpuscle to the periphery and then back again. When both filaments tear, each may roll up abruptly into a globular mass that comes to rest on the edge of the corpuscle (Fig. 13). These globular masses may be motionless after their formation; one or the other may show a quivering rotating movement and may even separate partially into two divisions; or they may change their position relative to each other on the periphery of the corpuscle. In older blood preparation the globules may appear on one of the flattened surfaces of the red cell. Their diameter seems to vary between 0.3 to 0.8 μ . The larger globules are generally less refractile than the smaller.

Instead of changing into a globule, one or both of the filaments may shorten and thicken during a period of minutes and become more refractile; the outline remains sharp but a nodular thickening may slowly appear at each end thus forming a dumbbell (Figs. 1, 2, 3). Such a rod may be apparently motionless; it may bend stiffly, swaying from side to side and maintain the same point of fixation; or it may exhibit a general fine quiver that was definitely referable to a rapid rotation around its long axis. Occasionally the end of such a rod may be terminated by a long, thin thread that undulates, twists and even lashes in all directions. The tip of such a thread describes circles, ovals and figures-of-eight, and rotates at one time to the right and at another to the left. The rods themselves now and then exhibit transitory, faint, diagonal striations on a portion of their length.

Another remarkable and frequently observed change is the conversion of a filament into a chain of refractile beads. This may be preceded by a period of increased undulatory swaying, by a general tremor, or the filament may be apparently motionless. Suddenly the observer notes a series of slight rhythmical twitches, and with each twitch the filaments shortens and a spherical bead appears, each bead separated from its neighbor by a short and equal length of filament. The beads form separately, beginning in the periphery. The entire filament may be converted into a chain of beads within 1 second, or several minutes pass slowly before the beading has reached the corpuscle. At other times the process pauses temporarily after one-half to two-thirds of the filament has been turned into beads, but sooner or later it begins again and the remaining section becomes beaded; here again the first bead appears in the periphery of the unchanged section and proceeds to the corpuscle (Figs. 14, 15, 16). The shortening of the filament is chiefly caused by the beading, aided perhaps at times by some thickening of the interglobular sections; in some cases, however, the sections connecting the beads may be exceedingly thin (Fig. 39).

When a filament tears away partly or completely from its peripheral anchorage, it may shorten but slowly and remain for a consider-

able period attached to the corpuscle as a long, actively twisting flagellum-like structure. The motility is strong enough to shake adjacent corpuscles as well as the parent corpuscle itself. In numbers of instances the peculiar quiver of a corpuscle and the irregular tremor of its neighbors betrayed the presence of filaments that became visible only upon careful search. In a corpuscle with several filaments, various stages of shortening may be seen: thus a crenated red corpuscle displayed at one time a chain of beads, a refractile rod, a refractile globule and two actively lashing and squirming long filaments.

The beads are moderately refractile, apparently homogeneous, round, measure about 0.3 to 0.4 μ in diameter and are equally spaced on the filament; they are apparently not doubly refractile when examined by polarized light. After its formation, the chain of beads may extend motionless from the periphery of a red corpuscle; it may sway and undulate stiffly; it may execute extremely lively movements, or all these reactions appear at different times. If the movements are lively, then the chain rotates, squirms, sways and may form traveling loops, the whole moving as a supple unit in all planes (Fig. 40). The terminal bead may be observed rotating occasionally to the right and at other times to the left. At times, a terminal bead or beads may be twisted off from the parent string during inspection; such a bead or group of beads then reels about for a variable period, and the single beads resemble a particularly active bit of blood dust (Figs. 40, 41, 42, 43).

Chains of spindle red corpuscles frequently occur where each one is linked to its mates by a filament of varying length. These connecting filaments lengthen and shorten, but shortening predominates so that finally the spindles are connected by short, thickened refractile rods which may be immobile or exhibit a fine, almost imperceptible quiver. The terminal filaments of the chain may be longer than the other connecting pieces. Sooner or later, one or the other terminal filament breaks and exhibits some, or many, or all of the changes described above. In one instance, upon rupture of a terminal filament in a lengthy chain of spindle corpuscles, the cells were seen rearranging themselves almost instantaneously into a typical rouleau; in this rouleau there was no sign of any filament, nor were refractile globules detectable.

There is evidence that the filament issues through a short prolongation of the surface layer. In some cases where the anchoring filaments ruptured simultaneously at the corpuscle, that corpuscle condensed into a microcyte and the former sites of the filaments were now occupied by stubby, pigmented plugs with square ends (Fig. 10). These plugs had the same dense hemoglobin tint as the microcyte itself, and disappeared rather promptly. In one case the process of disappearing was slower and there it was seen that the plugs were tubes.

Structure of the Filament. The filaments are composed of fine fibrils twisted around each other like the strands of a rope. This may be readily seen if filaments are carefully observed. It may be noted that a particular filament is suddenly shaken by a slight jolt and that coincident with this jolt a newly formed, small refractile pellet appears that swings around the main filament. Close inspection shows the pellet to be connected with the filament by a tenuous, barely perceptible fibril. Further observation shows that the pellet revolves around the parent filament with increasing amplitude of swing until it finally rotates on its own pedicle from the base of the filament (Figs. 21 to 24). After a while, the pellet or pellets, for several may be formed, may again twist their stalks around the main filament and finally produce an appearance that is almost identical with the one seen at the start (Figs. 21, 25). The time consumed was 10 to 15 minutes in one instance. The maximum number of pellets ever developed from one filament was five (Figs. 21 to 25).

Further evidence that a filament is composed of twisted fibrils is furnished by the behavior of free filaments in oxalated blood. In an alkaline medium, the unattached rod may slowly swell, rotate, and separate into several distinct strands. In one case, the end of the filament rotated and separated into three components revealing a left twist.

Each of the fibrils is composed of still finer, invisible subdivisions. Such invisible subfibrils are readily detected by their effect upon the attached corpuscle. For example, a red corpuscle is seen changing slowly to a spindle and yet the most careful examination may fail to detect any cause until gradually two filaments appear that are attached one to each apex of the spindle. Even after the filaments become visible, they may seem to end free in the serum and yet the spindle corpuscle may be rotated on its long axis, thus demonstrating that the filaments are anchored and that their peripheral sections are composed of invisible subfibrils (Figs. 26 to 30).

Further evidence is furnished by the persistence of a nipple on a red corpuscle whose filament has rolled up into a ball (Fig. 13). If all subfibrils have been torn, or if too few subfibrils remain to distort the indicator cells by their pull, then the corpuscular surface will round out to its normal contour and this is shown by the rolled-up filament at the upper pole of Figure 13. If, however, a pointed nipple remains, then invisible subfibrils must still be present in sufficient number to overcome the tension of the surface layer and stroma of the red corpuscle; this is shown by the lower pole of Figure 13.

Another piece of evidence is revealed by the observation that polyangular corpuscles are shaken at times by a twitch and with each twitch one of the angles of the corpuscle rounds out; a globule may or may not appear at the site of the former angle. Here the

invisible anchoring subfibrils apparently broke and permitted the corpuscle to resume a more normal shape.

The filaments are not sticky: red corpuscles swept against them by a local current do not adhere even momentarily. Nor does the filament stick to the surface of its own corpuscle when the latter has rolled over a section of the filament; such corpuscles were smoothly rolled back by the shortening filament. The fibrils also do not stick together (Figs. 21 to 25). It seems probable that the invisible subfibrils too are not sticky.

Filaments may disappear and yet some of their invisible subfibrils apparently remain present; this is indicated by the reappearance of visible filaments that had disappeared, and by the reestablishment of a former contour (Figs. 50 to 55).

That the filaments rotate around their long axis, producing a twisted, stranded arrangement of the fibrils, has already been mentioned and some evidence sketched in Figures 21 to 25; furthermore, the diagonal striation of their basal portions indicates a left or a right twist and it has also been noted that the chain of beads rotates to the right and then to the left. The best evidence, however, for rotation of the filaments is again supplied by the red corpuscle: these are frequently suspended between two filaments and such corpuscles may be seen rotating on their long axis so that a view on the flat changes to a view on edge and back again (Figs. 26 to 34).

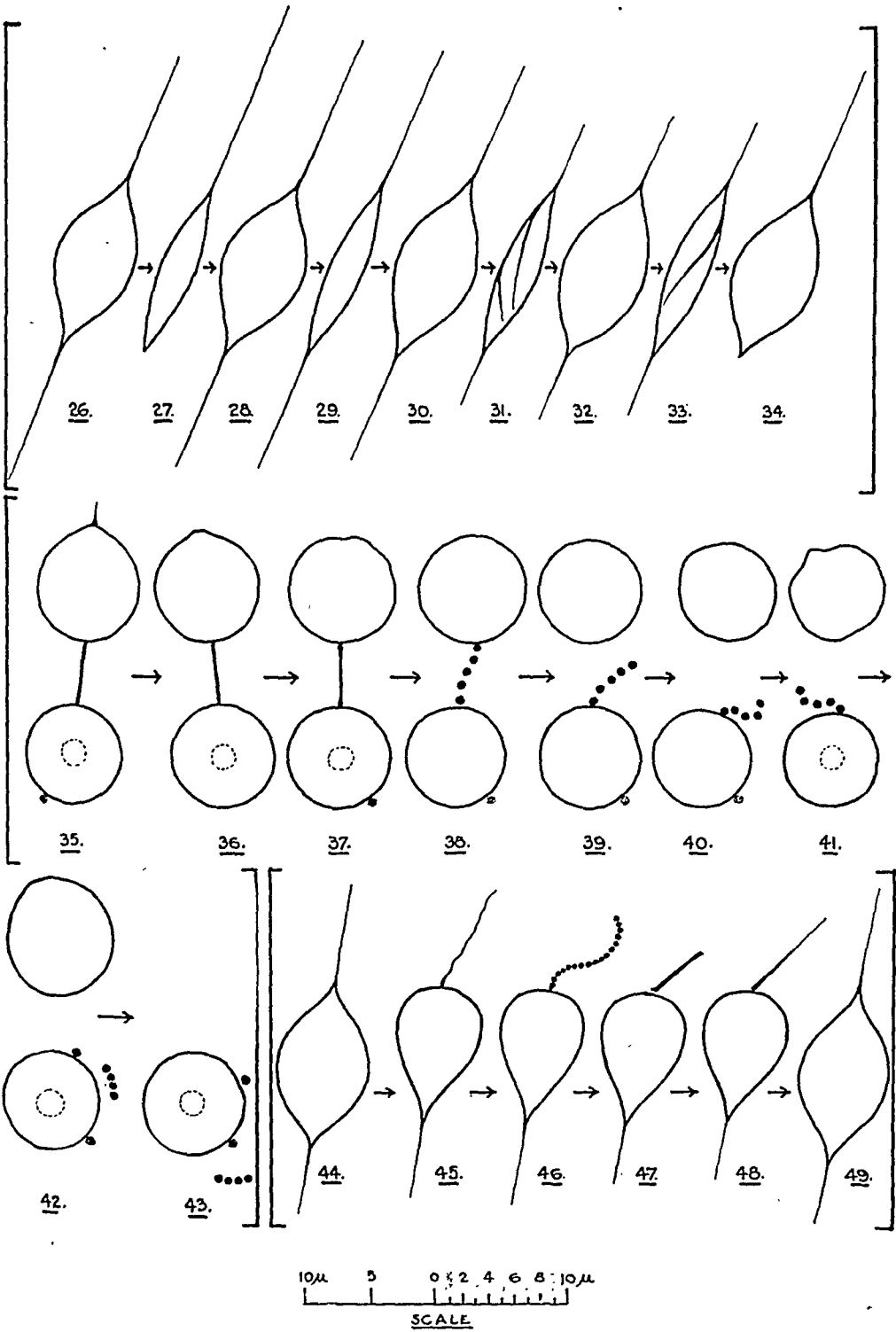
LEGENDS FIGS. 26 TO 49.

FIGS. 26 to 34, inclusive.—Dog, ♂, X2-135; hemoglobin, 80 per cent (Dare). Filariae present; sensitized with horse serum subcutaneously. 2.12 P.M., hanging drop, no addition; 2.20, spindle cell, long filaments (Fig. 26); lower filament no longer visible; becoming narrower (Fig. 27); 2.23, gradually becomes wider again, moves slightly upward in field, lower filament visible (Fig. 28); becoming narrower (Fig. 29); 2.27, again widens, typical spindle; lower filament shorter (Fig. 30); becomes narrower with folds, left twist (Fig. 31); 2.29, has changed back to spindle form (Fig. 32); 2.30, again narrow with single fold in body (right twist) (Fig. 33); 2.31, changes to typical spindle; lower filament not visible (Fig. 34).

FIGS. 35 to 43, inclusive.—Human, ♂, X2-100; hemoglobin, 85 to 90 per cent (estimated). 2.29 P.M., hanging drop with $\frac{m}{8}$ sodium oxalate; 3.18, 2 reds linked together by a refractile filament bar; lower red with marked dells and single globule on periphery; hemoglobin good in both; bar motionless (Fig. 35); 3.21, bar sways, rotates, outline smooth; 3.25, upper filament disappeared; bar very refractile; appears motionless (Fig. 36); 3.37, connecting bar again sways, rotates, looks faintly striated at times; ends of bar slightly knobbed (Fig. 37); 3.50, bar twisting and squirming actively; 3.57, bar changed into a beaded chain (Fig. 38); 3.57½, chain separates from upper red during inspection; vibrates actively (Fig. 39); 3.59, chain rolls about actively (Fig. 40); 4.02, upper red shows no dells; lower red round with strong dells; beads vibrate, twist, roll up actively into a ball and straighten again (Fig. 41); 4.06, beads connected by a very fine thread; 4.08, chain broke away from red corpuscle (Fig. 42); 4.11, free section sways, quivers, rotates to right, then to the left, tumbles about (Fig. 43).

FIGS. 44 to 49, inclusive.—Human, ♂, X3-67. 3.14 P.M., hanging drop; finger pricked through drop of saline; 3.15, spindle cells frequent; darting across field, filament changing to refractile globules; 3.40, free filaments, motionless or actively twisting; on thickening become motionless; 3.50 to 4.15, spindle red showed changes sketched in Figs. 44 to 49, inclusive.

The direction of rotation of the corpuscle may be determined when the rotating action of the filaments produce folds in the corpuscle: in Fig. 31 a left-handed twist is shown, while Fig. 33 exhibits a right-handed one. The twist of the corpuscle, however, merely indicates that its polar ends are



FIGS. 26 TO 49.

being rotated at unequal rates by the filaments and gives no information about the direction of rotation of the filaments themselves. Thus the left twist of Fig. 31 could be produced by a left-handed rotation of the upper filament, accompanied by a right-handed rotation of the lower filament; but the same effect would appear if both filaments rotated at unequal speeds to the right, the lower filament traveling faster than the upper one; another possibility is that both are rotating to the left with the upper filament moving faster than the lower one. If the speed and direction of rotation is the same and if both filaments exert the same twisting effect upon a corpuscle free to rotate, then no folds will be produced and a view on the flat of the corpuscle will change smoothly into one on edge (Figs. 26 to 29). Herrick perhaps saw the formation of folds in fresh blood of sickle cell anemia; he describes red corpuscles "rolled up as it were into a long narrow bundle" (p. 519⁵).

The degree of rotation suffered by the corpuscle is difficult to determine: Figs. 26 to 30 may show a complete revolution of 360°, or the same appearance could be produced by a turn of 90° in one direction followed by a 90° turn in the opposite direction. Similarly, Figs. 30 to 32 may mean a turn of 180° to the right, or a 90° turn to the right followed by a turn of 90° to the left.

Throughout the rotations sketched in Figs. 26 to 34, the corpuscles moved only once and that was slight, in an upward direction, and the upper filament shortened at the same time; the length of the spindle remained the same throughout the 10-minute period and the only change noted was a temporary increase in hemoglobin density while the corpuscle was on edge. These facts indicate that the undoubted rotation of the filaments caused no marked compression and loss of content of the corpuscle and that the compensatory rotation of the corpuscle itself was probably only through a 90° arc and then back to its former position. Similar observations were made in a specimen of human blood, 24 hours old, where the rotations of a spindle were watched for 5 hours; here (X3-109) no shortening had occurred after 2 hours, and after 5 hours the long diameter had decreased only 2.5 μ from its original length of 13 μ .

Fate of the Filament. The filaments often do not persist after their formation. The filament may roll itself into a ball and then disappear within 30 minutes or less (Figs. 50 to 53); the ball may persist for hours, being visible even after the corpuscle has laked, or it may uncoil itself again into a filament. Whether or no the ball was dissolved by the serum or by the corpuscle, or by both, could not be decided. A motile filament may gradually change to a linear, club-shaped, refractile, immobile mass that finally separates from the corpuscle; a series of this type in oxalated guinea-pig blood is sketched in Figs. 66 to 70.

A filament may shorten somewhat and lose its connection with the corpuscle. The movements executed now are different; instead of moving smoothly and with seeming coördination, the loose filament often rolls, twists and tumbles about, and behaves as if several independent foci of activity were present. These erratic movements are lively at first, but gradually become slower while

the filament itself shortens and thickens irregularly until finally a club-shaped, nodular, slightly refractile mass lies motionless in the field. Such masses may persist for hours.

Instead of forming immobile masses, the loose filaments may maintain their general shape for a long time. Thus a 24-hour-old specimen of human blood diluted with saline-oxalate (X3-66) showed many loose filaments with rounded ends that rotated and undulated fairly actively; their ends described circles, ovals, and apparently rotated alternately to the right and left; occasionally faint diagonal striations, either right or left, were visible for a short time along their length. Their progress was irregular and they seemed to slip sideways as much as they moved forward; in length and thickness they varied between 25 by $0.25\ \mu$ and 10 by $0.5\ \mu$. The shorter, thicker filaments in general exhibited only a swaying motion and their outline was not as clear-cut as in the more motile filaments. Such filaments were observed for 2 hours and no significant change occurred; their ultimate fate is unknown. These vermiculoid filaments were probably of the same type that Kite described (p. 326³).

When the filament forms a chain of beads, the terminal beads may be thrown off during inspection either singly, in groups, or the entire chain may separate from the corpuscle (Figs. 40 to 43). The loose bead or beads quiver and rotate erratically and resemble blood dust. A free chain of beads may become motionless after a time while increasing in bulk with decreasing motility and then it may disintegrate. This was clearly seen in a filament of normal rabbit blood whose transformations had been followed for more than 3 hours (Figs. 14 to 20); here a motile filament changed to a chain of beads and this became an immobile linear, slightly refractile mass which separated during inspection into smaller immobile pieces.

During the final changes just described, an interesting development occurred. After the linear mass had formed, one of its ends suddenly liberated a small, clear globule which either rose or fell from view. A similar observation was made in oxalated rabbit blood 4 hours old: a loose, motile filament became immobilized and during observation its middle portion swelled and liberated a small globule; here also it was impossible to tell whether it rose toward or fell away from the observer. No statement may be ventured about the nature of these curious globules.

Reversibility of Changes in the Filament. Some of the prominent changes observed in filaments are reversible. Thus a long, actively motile filament was seen darting suddenly toward its origin and coming to rest as a ball on the rounded border of the corpuscle. This form was maintained for a number of seconds, when abruptly the ball uncoiled itself into an actively lashing, rotating, flagellum-like filament.

In another example one filament of a bifilar corpuscle suddenly relaxed so that the corpuscle flattened to a pear-shape, and at the

same time the relaxed filament thickened moderately and became actively motile; this filament then changed abruptly into a squirming chain of equally spaced beads; now the chain of beads slowly became motionless, the beading grew less and less distinct and shortly an immobile, refractile, sharply outlined rod projected from the border of the corpuscle; this rod in turn gradually elongated and with this elongation the flattened surface of the corpuscle became stretched into a nipple; finally a spindle-shaped corpuscle was again taut between two filaments, presenting a picture like that seen in the beginning (Figs. 44 to 49). These events happened within 15 to 20 minutes in human blood 1 hour old and diluted with saline solution.

In a different preparation of human blood, 2 hours old, a chain of beads was seen straightening into an actively twisting and swaying filament; after 18 minutes this filament again shortened into a chain of beads.

Origin of the Filament. When the filaments were first seen in action, their motility was so impressive that the presence of parasites was suspected. This surmise was discarded as soon as filaments were found in practically every sample of blood from man, dog, rabbit and guinea pig. It was then assumed that they represented an early stage in the development of fibrin from plasma fibrinogen. Here again observations arose that could not live in peace with this assumption. For example, motile and contractile filaments were

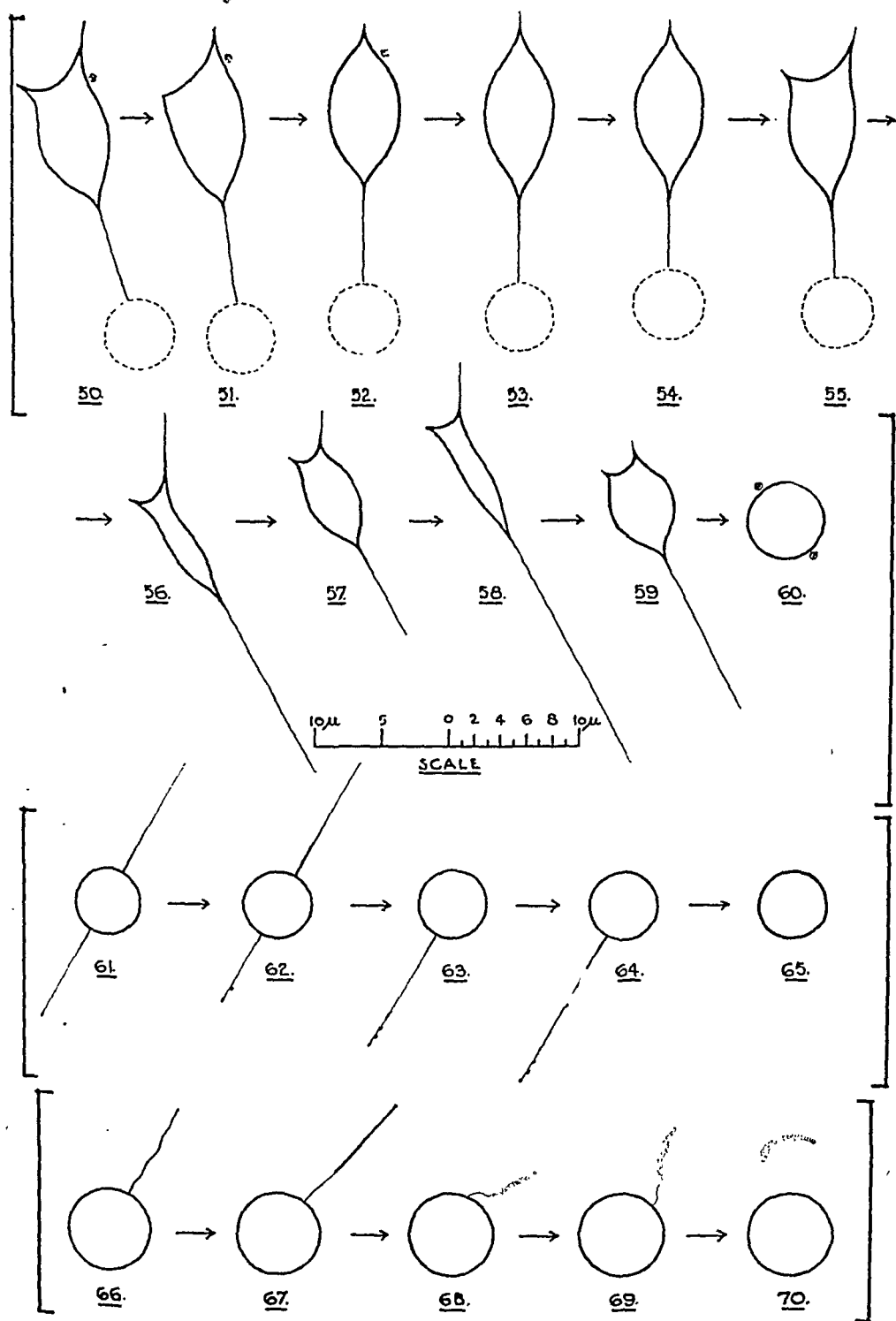
LEGENDS FIGS. 50 TO 70.

FIGS. 50 to 60, inclusive.—Human, ♂, X3-16; hemoglobin appears normal. 2.54 p.m., hanging drop, no addition; 2.55, spindle reds present; 3.14, vase-shaped red corpuscle with 3 filaments, lower one anchored to a microcyte shadow; refractile globule near upper angle (Fig. 50); 3.17, slight changes in contour; contents of red flickers; 3.25, refractile globule present (Fig. 51); 3.27, perfect spindle; globule at 1 o'clock present; no globule visible at former angle at 11 o'clock; no motility seen (Fig. 52); 3.33, refractile globule at 1 o'clock becoming smaller; lower filament slightly fuzzy at base; 3.38, refractile globule barely perceptible; 3.40, no refractile globule visible; hemoglobin tint normal; no motility or beading of filament (Fig. 53); 3.46, hemoglobin, no change (Fig. 54); 3.49, sudden appearance of filament at 11 o'clock; corpuscle same as at 3.14 (Fig. 50); 3.52, vase-shaped corpuscle; contents flicker; temperature, 69° F.; 3.59, corpuscle slender; microcyte shadow not visible; no motility or beading (Fig. 56); 4.07, lower filament shorter, looks fuzzy with diagonal striations (Fig. 57); 4.10, corpuscle lengthens and narrows (Fig. 58); 4.12, red becoming smaller; lower filament not visible; 4.20, hemoglobin denser; lower filament again visible (Fig. 59); 4.26, dense microcyte, with 2 refractile globules at poles; not doubly refractile; motionless (Fig. 60).

FIGS. 61 to 65, inclusive.—Guinea pig, ♂, 620, X3-32; hemoglobin not read. 10.07, hanging drop from heart blood; 10.08, spindle and angulated reds present; blood shadows; 10.13, microcyte, dense hemoglobin; 2 filaments at opposite poles; lower filament with small glistening mass at tip (Fig. 61); this microcyte passed through the stages sketched in 7+ minutes; no globules formed on microcyte.

FIGS. 66 to 70, inclusive.—Guinea pig, ♂, 265, X2-98; hemoglobin, 114 per cent (Dare). 2.18, hanging drop with $\frac{m}{8}$ sodium oxalate; 2.27, jerks seen in field; 3 o'clock, many linear, motionless, moderately refractile masses, often club-shaped; occasionally slightly granular; 3.22, formation of such masses from a filament observed (see sketches 66 to 70, inclusive). The entire process occurred in 8 minutes; 3.45, outline of mass slightly more irregular.

seen after 24 hours when the formation of fibrin should have been complete. Similarly, the observation that 3 such filaments could attach themselves suddenly, simultaneously and with equal spacing on one red corpuscle (Figs. 7, 8, 9) was always a cause of



FIGS. 50 TO 70.

pained astonishment until a closer examination of serum fibrin threads revealed definite morphologic and functional differences between them and the motile filaments.

Typical fibrin threads of plasma origin may be seen within 2 or 3 minutes after making a hanging drop and are readily observable in the spaces between corpuscle aggregates. These spaces may or may not show a platelet. The fibrin threads are at first straight, slightly angular on optical cross section, sharply outlined, moderately refractile and decrease gradually to a pointed tip. The fibers form a loose, irregular network and cross each other at various angles. When a platelet or remnant of a platelet is present, it usually lies within a radiating system of such threads. After 15 to 30 minutes the space has definitely decreased in size, the network is closer-meshed, the threads have become curved or sharply angulated, and some may appear flattened like a ribbon. At times the ribbon-like threads appear split along a portion of their length. During this time the most careful and continuous observation failed to detect any sign of motion in characteristic fibrin threads. Occasionally a spirally twisted fibrin thread was seen but their formation was never observed.

Actively motile filaments may be seen squirming and lashing about in a nest of fibrin threads; these filaments conformed in shape and function to those attached to red corpuscles and were quite different from ordinary fibrin threads.

With dark-field illumination, fibrin threads appeared that were invisible under bright-field conditions. Their form and behavior was the same as that described except that a blurring of the originally sharp outline became noticeable in some threads after 15 to 30 minutes. Here again no motility was seen in a typical fibrin thread.

Since the form and behavior of typical fibrin threads and of filaments were different, the supposition of their common origin was abandoned. Red corpuscles were next considered as the source and a test was made as follows: 0.50 cc. of blood was dropped directly from the vein into a centrifuge tube containing 10 cc. of Ringer saline solution. The suspension was shaken and centrifuged for 5 minutes in a Shelton electric centrifuge. The supernatant liquid was decanted, replaced with the same amount of washing liquid, shaken vigorously and recentrifuged for another 5 minutes. This procedure was repeated 4 to 6 times with each sample of rabbit and guinea-pig blood. Then some of the precipitated red corpuscles were examined in a hanging drop. In all of these tests typical filaments were observed. The filaments became visible about 30 to 45 minutes after making the hanging drop. In one instance none was detectable for 2 hours, but 24 hours later the same drop displayed slender filaments that connected and deformed red corpuscles. The filaments were much thinner and fewer in number than those observed in normal blood, but they exhibited a typical activity and often changed into a squirming chain of beads. Since all plasma had probably been removed by a drastic washing, and since no other formed elements were present, the inference is justified that the motile filaments are formed from some component of the corpuscle itself.

Though the evidence indicates the erythrocytic origin of the filaments, it does not indicate that the red cells are the only source. It is probable that motile filaments may arise from platelets, and a number of times these were seen attached to platelets in oxalated or heparinized blood. In one example, a slender filament, actively whipping about, issued from the tip of a short, refractile, smoothly contoured rod that was anchored to a platelet. In another case, the threadlike prolongation of a platelet was seen 2 times throwing off a small refractile granule at the point where the thread joined the platelet. Both observations were made on human blood. Motile filaments were also noted on rabbit platelets.

Occasionally slender threads were observed issuing from leukocytes, but these differed in refractility and motility from typical filaments.

Effect of Anticoagulants. The action of sodium oxalate, hirudin and heparin was tested in 19 experiments; the oxalate was used in $\frac{m}{8}$ strength and the other two substances were dissolved to varying concentrations in physiologic saline solution. The heparin experiments were made exclusively with human blood; with the other anticoagulants, blood from man, rabbit and guinea pig was used.

The main object was a comparison of the effect of the anticoagulants upon the formation of fibrin threads and filaments. The study shows that 10 out of 19 tests exhibited little or no fibrin, while typically motile filaments attached to red corpuscles were present (4 oxalate, 3 hirudin, 3 heparin tests); in 5 of these 10 tests no fibrin at all was seen. In 3 tests both fibrin and filament were absent (1 oxalate, 2 hirudin). In 6 tests both fibrin and filaments were seen, but both were definitely reduced in amount (3 oxalate, 1 hirudin, 2 heparin). These tests gave the distinct impression that the anticoagulants reduce the production of both fibrin and filaments; furthermore they also indicate that this reduction is more noticeable with fibrin than with the filaments.

The motility and contractility of the filaments in most of these experiments were not perceptibly altered. In a number of heparin experiments, however, a surprising sluggishness of contraction was seen. For example, in heparinized human blood (X3-70) spindle-shaped corpuscles had been formed within 5 minutes and rupture of the peripheral end of the filaments was first observed after 13 minutes. Upon rupture, such filaments rolled up leisurely into a ball, or formed a chain of beads or contracted into a thick, refractile rod with terminal knobs. If a filament was transformed into a ball, then simultaneously the spindle corpuscle flattened and glided slowly as a pear-shaped body, apex in advance, toward the side of the field where the intact filament was anchored, revealing that the intact filament also was shortening with apathy. This type of shortening is thus in sharp contrast with that observed in normal blood where the torn filament rolls up with the speed of a stretched spring that has been released, and where the corpuscle is often fairly hurled across the field by the unopposed pull of its intact filament. Still other variations occur: if a chain of beads develops,

then the beads may be oval or sausage-shaped, and each bead is larger than those seen in ordinary blood (Fig. 2); if a rod is formed, its refractility seems greater than that generally seen, and the rod may exhibit a slight but definite yellowish color. The rate of shortening is seen in Figures 1, 2 and 3: 2.5μ in 9 minutes.

Discussion. The following statements represent an attempt to tie together the various observations recorded in this paper and to place them tentatively in the general blood picture; they are brief because space restrictions forbade development, and for the same reason some interesting and important work, for example the micrurgical studies of Seifriz on various types of erythrocytes,⁹ had to be neglected.

It is possible that the parent substance of the filaments is identical with the hemoglobin-free, fibrinogen-like material that Horino¹⁰ isolated from washed red corpuscles, because this parent substance lies inside of the red corpuscle and because the anticoagulants decrease or abolish the formation of filaments. It is conceivable, furthermore, that the clear interstromatic liquid of red corpuscles (p. 558²) contains the hemoglobin-free parent-substance of the filaments. The formation of filaments by drastically washed corpuscles indicates however the existence of some difference between this intracorpuseular substance and plasma fibrinogen.¹¹

The parent substance of the filaments could be expelled through the surface layer by increased intracorpuseular tension. Sound evidence that the hemoglobin stroma of red corpuscles may contract powerfully has been given (p. 558²).

If the surface layer of red corpuscles is assumed to be an interlacement of stroma fibrils (p. 562²), then the passage of the parent substance of the filaments through the submicroscopic interstices of the surface layer would produce invisible subfibrils which could be changed to a fibrinlike material after their exit. The intertwining of subfibrils could form fibrils and they in turn filaments. The twisting together is probably aided by the spiral turn given to the subfibrils when the liquid parent substance is forced through the interstices of the surface layer.

The powerful shortening of the filament is caused at least in part by rotation around its long axis, and is readily imitated by twisting an elastic rubber thread. The rotation in the opposite direction is attributable to an incomplete elastic recoil. This elastic recoil may be caused by repeated, relative decreases in the amount of material expelled per unit of time by the corpuscle (see lower filament of Figs. 26 to 34). The active rotation is partly referable to the spiral movement given the subfibrils by their expulsion through the interstices of the surface layer.

The formation of a single ball when a filament tears away from its peripheral anchorage is apparently due to the elastic recoil of the strongly twisted filament into a skein; a similar form is produced momentarily when one end of a twisted rubber thread is suddenly released.

The formation of beads at equal intervals on a shortening filament cannot be fully explained at present, but apparently rotation and successive ruptures of the elastic anchoring subfibrils are primary factors.

The reversible changes of a filament into a ball, a rod or a chain of beads indicates clearly that these changes do not necessarily alter the essential structure of the filament.

The more or less slow disappearance of filaments without the formation of globules on the corpuscle (Figs. 9, 10, 11; 61 to 65) is apparently caused by a gradual or abrupt stoppage in the supply of material for making the filament. Under these conditions, rupture of the strained filament occurs at the corpuscle and the severed filament recoils to its peripheral anchorage.

The stoppage of material for spinning the filament may be caused by an increase of tension in the surface layer to such an extent that the parent material of the filaments cannot pass through the interstices.

The tubular stubs noted occasionally (Fig. 10) may be interpreted as extensions of the surface layer of the corpuscle produced by the pull of the filament, and in a certain sense may be called spinnerets.

Since the filaments may go into solution, it is obvious that the serum will contain material extruded by the red corpuscles even though no laking whatsoever occurs.

What rôle the filaments play in forming a soft clot or in retraction of the coagulum cannot be stated at present. It is, however, undeniable that the filaments may be strikingly motile; that they can shorten powerfully, drawing red corpuscles together into chains and rouleaux, and that they can deform red corpuscles. It may be furthermore suggested that the mechanical activity of the filaments aids not only by converting plasma fibrinogen into fibrin but also by felting the fibrin threads into a mass, just as hair is felted together by a mechanical beating. Attention may again be called to the fact that no motility of serum fibrin was ever seen.

Red corpuscles may not be the only source of the filaments and some evidence has been submitted indicating that they may be formed by platelets. Whether or no leukocytes can form filaments is an open question; Kite makes no distinction between the undulatory processes of red and white corpuscles (pp. 323, 327³); my own observations are few, and do not support Kite. It may be noted that Leo Loeb observed the formation of long threads in pseudocoagulation of *Limulus* amoebocytes and that he attributes the physical characteristics of fibrin to these threads.¹²

Summary. 1. The living red corpuscle of guinea pig, rabbit, dog and man, in hanging-drop preparations produces almost colorless, tapering, elastic filaments varying in number from 1 to 5 and in length from 5 to 75 μ .

2. Filaments may apparently arise from platelets.

3. The filaments may appear within a few minutes after a hanging drop is made and be readily detectable for more than 24 hours; they are composed of twisted fibrils which in turn are composed of separately invisible subfibrils; the filament, fibril and subfibril are not sticky; the filament is motile and rotates around its long axis to the right and to the left, one direction predominating thus ultimately causing a shortening; the filaments anchor themselves peripherally to other red corpuscles, to blood shadows, to platelets, to the edge of the drop; their shortening distorts and compresses red corpuscles into various shapes and may produce a microcyte with dense hemoglobin content; the filament may tear peripherally and roll up into a ball, or change into a chain of refractile beads or thicken into a refractile rod; all these changes are reversible; the beads and the filament are not doubly refractile; both filaments and beads may appear free in the serum and execute active movements; single free beads resemble blood dust, but are more lively at first; the formation of filaments is decreased or abolished by sufficient amounts of sodium oxalate, hirudin and heparin, but filament formation is more resistant to these substances than fibrin formation from plasma fibrinogen.

4. These filaments are probably the agents that cause cell deformation in sickle-cell anemia.

5. No contraction or intrinsic movement of typical fibrin threads from plasma fibrinogen was ever seen.

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A NEW JERSEY OUTBREAK OF TRICHINOSIS WITH REPORT OF A CASE COMPLICATED BY FEMORAL THROMBOSIS.

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WHILE infestation with *Trichinella spiralis* in a degree sufficient to produce definite symptoms is, perhaps, infrequently recognized, extensive outbreaks are relatively uncommon in the United States, although, during the past 3 or 4 years an unusually large number of cases have come to light.

The large number of individuals affected in the outbreak to be described, together with the unusual and not readily to be explained occurrence of femoral thrombosis in one of the cases, seems to warrant description and record.

As illustrating the ease with which, in the absence of a suggestive history or typical findings, the possibility of trichinosis may be overlooked, the events will be described as they occurred.

Case Abstract.—E. P., Italian male, hotel employee, aged 42, was admitted to the medical ward of this hospital March 4, 1933, on the service of Dr. Samuel Barbash, the chief complaint being fever and malaise.

The patient seemed dull and apathetic and did not coöperate very well with attempts to obtain a history. It was ascertained with some difficulty that 1 week before admission he had had "a cold and ached all over."

After being sick 1 week in bed he was seen by Dr. Merendino, who learned that he had been delirious on several occasions and on others had been found lying on the floor where he had fallen out of bed. At this time he was very sluggish mentally and because of this and the sustained fever he was sent to the hospital as a possible case of typhoid fever.

On admission the temperature was 102°, pulse 110, and respirations 26.

LABORATORY REPORTS.—The Widal, Wassermann (Kolmer quantitative), and precipitation (Kline) tests were negative. Blood sugar, 100 mg. per cent; urea nitrogen, 18 mg. per cent; creatinin, 1.5 mg. per cent. The urine, except for the presence of 5 mg. per cent of albumin and a faint trace of indican, showed nothing of interest. Hemoglobin (Haden) 13 gm. per cent (87.6 per cent); red blood cells, 4,490,000; color index, 0.9; white blood cells, 9800. Differential: Polymorphonuclear, 68 per cent; small lymphocytes, 23 per cent; eosinophils, 9 per cent. Blood culture gave no growth after 1 week incubation.

Nothing of interest occurred until 3 days after admission when, during the night of March 7, the patient complained of a sudden, sharp pain in the upper part of the left thigh, at the same time showing a fall in temperature to 97° F. The foot and leg soon became cold and there was apparently a spasm of the calf muscles. The following day he was cold, clammy, sweating profusely, anxious in his general demeanor, and complained of chilliness as well as of loss of feeling in the entire leg except the toes, and a line of demarcation began to appear a short distance above the knee. This, together with the absence of any femoral pulsation, amply corroborated the assumption of femoral occlusion.

While this diagnosis was easily made the reason for its occurrence was far from obvious, and in an endeavor to obtain additional information the patient's friends were interviewed by Dr. Barbash.

During the course of the investigation the woman with whom the patient boarded expressed her firm conviction that it was the result of something he had eaten at a birthday party, as a number of those who were present had also become ill shortly after.

On further inquiry it was found that the refreshments consisted of home-made Italian sausage and red wine and the nature of the patient's illness at once became obvious, especially when the eosinophil count rose to 16 per cent, and encysted trichinæ were demonstrated in the sausage meat.

The gangrene of the leg became progressively more marked, eventually extending to midthigh so that amputation became imperative despite the poor general condition of the patient. Amputation was done on March 14 and death occurred March 16.

AUTOPSY (partial).—The body is that of a well-developed adult Italian male apparently about 45 years of age. The skin has a definite pallor. The left leg has been amputated at about the middle of the thigh. The skin of the stump as far as the inguinal region is very tense, swollen and discolored, while the stump is malodorous and discharging pus. There is a mark of a venipuncture in the region of the left median basilic vein. There are no other external marks of interest.

Chest. Permission to open the chest was not obtained.

Abdomen. The liver is about normal in size. When cut it does not appear to contain an abnormal amount of blood. The cut surface has a somewhat granular appearance and suggests a moderate degree of fatty

metamorphosis. The gall bladder is filled with dark, viscid bile but otherwise presents no gross changes of moment.

The spleen is approximately $2\frac{1}{2}$ times the usual size and shows a large anemic infarct approximately 5 cm. in diameter involving the lower pole. The gastro-intestinal tract presents no gross abnormalities. The kidneys are approximately normal in size but the cut surface appears, perhaps, somewhat paler than usual.

The superficial tissues as well as the deeper structures of the left upper leg appear to be markedly swollen and edematous, and gas bubbles are seen on incision.

The left femoral and left external iliac arteries are completely thrombosed all the way up to the point of bifurcation from the common iliac, the clot, when partially expressed, showing fairly well-marked organization, thus evidencing its antemortem origin. The vessel walls do not show any gross or macroscopic abnormalities. No gross evidence to explain the circulatory block could be demonstrated.

ANATOMICAL DIAGNOSIS.—(1) Trichinosis (clinical and laboratory diagnosis); (2) splenic infarct; (3) fatty metamorphosis of liver (?); (4) amputation (mid thigh) left leg; (5) gas bacillus infection and gangrene of stump; (6) thrombosis of left femoral and left external iliac arteries.

Cultures taken at autopsy from the liver, spleen, and heart blood gave no growth; the stump gave a mixed growth of *B. welchii* and *Staphylococcus pyogenes* (aureus).

Histologic examinations of material from the amputated leg gave the following findings:

Muscle. Sections show the presence of moderately numerous encysted trichinae, as well as inflammatory and degenerative changes in the muscle fibers.

Femoral Artery and Vein. Sections show organizing arterial and venous thrombi in which trichinae are not found. Cross and longitudinal sections of the arterial wall show no marked evidence of pathologic changes.

Clot from Femoral Artery. Sections show an organizing clot. Trichinae were not demonstrated.

As already stated, numerous encysted and partially encysted trichinae were found in sections of the sausage eaten by the patient, in muscle from the amputated leg, and in sections taken at autopsy of the diaphragm and muscle from the amputation stump. Sections from the liver presented the histologic picture of a moderate degree of passive congestion associated with diffuse and marked fatty metamorphosis; while those from the kidney exhibited occasional small focal hemorrhages and diffuse cloudy swelling.

The cause of death was obviously not trichinosis but the toxic absorption from the gangrenous leg coupled with the shock of operation and absorption from the infected stump.

The case derives its particular interest from the femoral occlusion, the occurrence of which it is difficult to explain as none of the usual incitants of this condition could be proved.

There was neither history nor evidence of trauma; clinical and laboratory evidence of disturbances in the coagulability of the blood were lacking; no signs of pathologic changes in the vessel walls could be found on microscopic examination, nor were there any evidences of blood stream infection or of pelvic inflammatory processes.

The question arises, was there any etiologic relationship between the trichinosis and the femoral block?

On the one hand, it is held by one of us (S.B.) that as no other reason for the arterial blockage can be found the fact of its occurrence in association with trichinosis cannot be disregarded nor the possibility of some direct—though admittedly inexplicable—relation entirely dismissed.

The senior author (R.A.K.) on the other hand, regards such an assumption as extremely unlikely and difficult to uphold. In the first place, while many thousands of cases have been recorded in the literature, such an association has never been reported. While this does not, of course, render the occurrence impossible, it is difficult to assume that, could trichinosis produce such an effect *per se*, it would never have been reported before.

Second, it is difficult, if not impossible, to imagine the mechanism whereby such a lesion could be produced as a result of trichinosis. While it is true that an essential feature of the disease, and one responsible for the persistence of its symptoms, is the dissemination of the larvæ by means of the blood stream, it is also true that in this stage the larvæ, measuring 100 by 6 microns, are no larger than the average diameter of a normal erythrocyte (7.5 microns) and hence pass freely through so fine a capillary network as that of the pulmonary circulation. In order to produce a block even in the capillary circulation, therefore, it is necessary to assume, first, the presence of larvæ in agglomerate masses of sufficient size to occlude the capillary vessels of the foot, and, second, that this having taken place, the thrombus gradually extended upward along the vessels without symptoms of any kind until it reached the femoral artery in the middle of the thigh, producing the sudden, sharp pain recorded in the history, which was then followed by the appearance of gangrene.

These assumptions do not seem tenable. In fact, the history of sudden, acute pain followed by coldness in the affected leg, which before this had shown no abnormality of any sort, is much more conformable with embolism than thrombosis and, on the grounds recited above, any direct etiologic relationship between the trichinosis and the circulatory occlusion is difficult, if not impossible, to predicate. It seems, rather, a fortuitous coincidence.

The elimination of trichinosis leaves the circulatory block unexplained. It is interesting, however, that one of us has previously recorded (1) the occurrence of an axillary thrombosis leading to gangrene and amputation of the arm in a patient admitted to the medical service for acute wood alcohol poisoning. While the *modus operandi* of this occurrence was far from clear, it was tentatively suggested that the thrombosis might have been the aftermath of some chemical, toxic action of the wood alcohol.

We refer to this simply because the patient who is the subject

of this report was said to have been a consistent drinker of "anything." On the other hand, there was no history of excessive drinking immediately preceding his admission and whereas the axillary accident occurred shortly after a profound poisoning with wood alcohol, in the present case the femoral occlusion occurred on the ninth day of the only illness from which he is known to have suffered immediately preceding his admission to the hospital. The cause of the circulatory catastrophe in the present case remains a mystery.

Outbreak of Trichinosis. The history of the outbreak, of which this patient was a part, while true to form as regards its essential details, is of interest because of the number involved.

On January 31, 1933, a pig was purchased by two Italian families jointly and killed on the same day, the meat being made into sausage on February 2, a small portion being pickled.

Home-made Italian sausage is usually made by chopping the meat into relatively coarse pieces which are mixed with large amounts of spices, packed into skins, and then hung up to dry for 2 or more weeks. The resultant product is a hard, highly-spiced product resembling salami or some kinds of German bologna.

The preparation of the sausage in question was completed February 2 but some of it was eaten 2 days later by one of the men who made it. On February 12 this individual became ill with what was regarded as "grippe" because of the fever and muscular pains.

On February 9 a birthday party was given by one of the families who had purchased the pig, the refreshments consisting almost entirely of red wine and the home-made sausage, which was not only freely eaten of by the guests but many also carried away with them a supply for future home consumption.

While one or two of those attending the party had rather marked gastro-intestinal disturbances very soon after, the outbreak proper began about 10 days later when, one by one, those who had attended it became sufficiently ill to send for a physician.

The first cases were seen on February 14 by Dr. Merendino, a mother and her daughter aged 12 years, complaining of vomiting, diarrhea, fever, and generalized myalgia which had not responded to home remedies. Calls for similar complaints then came thick and fast until 11 different patients were seen by Dr. Merendino. At the same time a number of similar cases were being seen by Dr. Louis Mackler to whom we are indebted for information concerning them as well as for cooperation and assistance in rounding them up for further study.

In all instances the clinical symptoms were in general the same varying degrees of gastro-intestinal disturbance associated with muscular pains and fever ranging from 99° to 104°.

In every case seen by both Drs. Merendino and Mackler the fever was ushered in by a chill of varying intensity. Nausea, vomiting, and epigastric pain were quite commonly complained of, while a

few of the patients presented signs of a bronchitis with the expectoration of a brownish, viscid sputum. The history of 3 patients records mental confusion and even delirium of short duration.

One of Dr. Mackler's cases had repeated epistaxis and another a marked subconjunctival hemorrhage.

Edema of the face and eyelids occurred—or, at least, was recorded as present—in only 2 cases, being marked in neither, but edema of the legs was very generally noted. It is of practical importance that this was difficult to detect while the patients were bedfast but easily recognized when they were out of bed, being quite marked and persistent and lasting in many instances, as did the muscle pains, up until the preparation of this report (April).

Albuminuria or casts were not found in any of the cases examined outside the hospital.

When the diagnosis of trichinosis was established, following the admission to the hospital of the patient with whom this report is primarily concerned, practically all those who attended the party were examined for eosinophilia with results given in the table following:

TABLE

No.	Pt.	Age.	Raw sausage.	Cooked sausage.	Sick.	Eosinophils, per cent.	Remarks.
1	G. del P.	43	Yes	..	Yes	32	Sick 11 days; fever, myalgia, edema of legs.
2	O. del P.	23	..	Yes	No	2	Son of Pt. 1; ate only cooked sausage.
3	Mary P.	28	Yes	..	Yes	11	Gastro-intestinal symptoms and myalgia.
4	Enrico P.	42	Yes	..	Yes	16	Ate large amounts of raw sausage; sick 9 days, then developed left femoral thrombosis and gangrene of leg; amputation, death.
5	Peter P.	38	Yes	..	Yes	23	Edema of legs; myalgia.
6	Patsy P.	40	Yes	..	Yes	10	Ate only small amount; slight symptoms.
7	Angelina P.	12	Yes	..	Yes	30	Gastro-intestinal symptoms; myalgia, some edema of legs.
8	Rose M.	12	..	Yes	Yes	26	Ate only cooked (heated?) sausage repeatedly; headache; malaise.
9	Albert M.	10	Yes	..	Yes	21	Chills, fever, myalgia, edema of legs.
10	Anacella M.	14	Yes	..	Yes	30	Chills, fever, cough, myalgia, edema of legs.
11	Enrico M.	42	Yes	..	Yes	41	Fever, edema of eyelids, myalgia, edema of legs.
12	Mrs. M.	42	..	Yes	Yes	56	Repeatedly ate large amounts of cooked (heated?) sausage; sick 17 days, facial edema, chill, fever, myalgia.

TABLE—Continued.

No.	Pt.	Age.	Raw sausage.	Cooked sausage.	Sick.	Eosinophils, per cent.	Remarks.
13	Peter F.	35	Yes	..	Yes	40	Sick 3 weeks.
14	John F.	20	..	Yes	No	3	
15	Frank F.	3	..	Yes	No	12	
16	Mary F.	5	..	Yes	No	9	
17	Louis S.	39	Yes	..	No	2	Ate very small amount.
18	Catherine S.	48	..	Yes	No	1	
19	Matteo V.	43	Yes	..	Yes	5	
20	Mrs. V.	30	Yes	..	Yes	40	Sick 3 weeks.
21	Baby V.	2	Yes	..	Yes	11	Appeared "cranky" and "fussy," not otherwise ill. Refused to walk for 10 days.
22	Tina C.	..	Yes	..	No	4	Ate very small amount.
23	John C.	..	Yes	..	No	0	Ate very small amount.
24	Philomena C.	..	Yes	..	No	1	Ate very small amount.
25	Benj. P.	50	..	Yes	Yes	9	Slight gastro-intestinal symptoms.
26	Caesar C.	30	Yes	..	No	1	Ate small amount, had immediate gastric distress, took purgative at once.
27	Mrs. di G.	46	Yes	Yes	No	0	Ate small amounts of both raw and cooked sausage, "cramps" for 2 days, not otherwise ill.
28	Giovanni M.	33	Yes	Yes	Yes	11	Myalgia and edema of legs.
29	Albert C.	30	Yes	..	No	4	Ate very small piece.
30	Jos. A.	36	Yes	..	No	0	Ate very small piece.
31	Guiseppe F.	36	Yes	..	Yes	37	Fever, malaise, myalgia, edema of legs.
32	Jean C.	35	..	Yes	?	3	Ate small amount of slightly heated sausage; mild gastric distress, mild myalgia (questionable).
33	Wm. C.	10	..	Yes	No	6	
34	Mrs. C.	43	..	Yes	No	0	
35	Benj. de M.	Yes	No	4	Ate only small amount.
36	Albert de M.	2	Yes	..	No	2	Ate only small amount.
37	Mrs. de M.	19	Yes	..	No	0	Ate only small amount.
38	Mrs. de F.	45	..	Yes	No	0	
39	Mary de F.	9	..	Yes	No	1	
40	Nick de F.	48	..	Yes	No	2	
41	Albert A.	11	Yes	..	Yes	19	Ate raw sausage supplied by playmate; sick 1 week, fever, myalgia.
42	Louis de J.	..	Yes	..	?	2	Attended party and ate small amounts of raw sausage; questionable myalgia.
43	Victor V.	4½	Yes	..	Yes	30	Same family as Nos. 19-20-21. Became ill much later; fever, myalgia, malaise.

It will be seen from the data given that of 28 individuals who ate raw sausage 17 (60 per cent) exhibited clinical symptoms and had eosinophilia of varying degree.

Of 17 persons who ate cooked sausage 4 (22 per cent) complained of symptoms of varying severity and 7 (40 per cent) exhibited eosino-

philia varying from 6 to 56 per cent, explainable by the fact that the "cooking" in many instances meant only the heating of the sausage.

Two individuals ate both cooked and raw sausage and hence appear in both groups. One complained only of "cramps" and did not show an eosinophilia when examined; the other complained of myalgia, presented edema of the legs, and had an eosinophil count of 11 per cent.

In view of the heavy infestation of the pig, as shown by the large numbers of encysted trichinæ in the sausage and meat examined, it is not improbable that some of those not presenting symptoms or eosinophilia when this report was written may do so later.

Through the courtesy of Benjamin Schwartz, Ph.D., Senior Zoölogist, United States Department of Agriculture, a trichinæ antigen was prepared for the conduct of intradermal tests after the procedure proposed by Bachman.² As many as possible of the group in this series will be tested by this method and the results reported in a separate communication.

It is not improbable that trichinosis in mild forms not clinically recognizable nor suspected may occur more frequently than commonly supposed, for it is impossible to regulate the home manufacture of pork products and, as in the present instance, the trichinous animal may appear perfectly well.

Extensive outbreaks of trichinosis in the United States are always associated with the consumption of home-made pork products.

No danger arises from the use of packer's pork products of the kind usually eaten without cooking as these, under Government regulation, must either be refrigerated at a temperature not higher than 5° F. for at least 20 days, or subjected to other treatment approved by the Chief of the Bureau of Animal Industry.

The efficiency of refrigeration, first established by the extensive investigations of Ransom, has been amply corroborated by other observers, the most recent study being that of Augustine³ showing that pork, in commercial quantities, may be rendered safe, as far as trichinosis is concerned either by rapidly lowering its temperature to -35° C., or by rapidly lowering the temperature to -18° C. and maintaining that temperature for at least 24 hours.

However, as an added precaution, essential in the case of home-made products, pork products not ordinarily eaten without cooking should be *thoroughly* cooked in all instances.

Data concerning the effect of pickling upon the viability of trichinæ are neither definite nor extensive. While the U. S. Bureau of Animal Industry has developed specific curing methods for special products containing the muscle tissue of pork these are not applicable to home-made products which, in the last analysis, are the most important source, not only of extensive outbreaks, but also of the perpetuation of the disease in the human being.

Summary. A case of trichinosis complicated by femoral thrombosis is reported together with the particulars of an outbreak arising from the ingestion of home-made sausage and involving 43 persons.

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THE BACHMAN INTRADERMAL REACTION IN HUMAN TRICHINOSIS.

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ALTHOUGH extensive outbreaks of trichinosis are uncommon in the United States an unusually large number of cases have come to light during the past 3 or 4 years and it is possible that more are unrecognized because of the mildness of the symptoms or for other reasons.

In 1928 Bachman^{1,2} described an intradermal reaction in experimental trichinosis which, apparently, has not been widely applied, if at all, to the study of this disease in the human being.

An opportunity to utilize the Bachman skin test in the study of human trichinosis arose during the outbreak described in the previous paper.³

Methods. The isolated, dried, and powdered trichinae larvae necessary for the preparation of the Bachman antigen were made available through the interest and courtesy of Benjamin Schwartz, Ph.D., Senior Zoölogist, U. S. Department of Agriculture, Washington, D. C., and the majority of those involved in the outbreak were induced to submit to the test through the coöperation of Drs. S. Barbash, A. G. Merendino and L. Mackler to all of whom acknowledgements are due for their assistance in making this study possible.

In the preparation of Bachman's antigen, 1 month after the infection of guinea pigs by the feeding of trichinous meat the animals are killed, the muscles containing encysted larvae separated, and the larvae isolated by artificial digestion.

The isolated larvae, after thorough washing in water, are then dried at 45° C., or *in vacuo* over sulphuric acid, and pulverized.

For use a 1 per cent solution of the dried powder is extracted by shaking in Coca's solution* and allowed to stand over night in the refrigerator.

The turbid fluid, which is stated by Bachman to be practically free from host protein, constitutes the antigen used for the skin test. The antigen furnished by Mr. Schwartz was made of larvae isolated by means of the

* Coca's solution: Sodium chlorid, 0.7 gm.; sodium bicarbonate, 0.05 gm.; phenol, 0.4 gm.; distilled water, 100 cc.

Baerman apparatus and was free from foreign protein by repeated passage of the larvæ in large volumes of water through the apparatus.

In the conduct of the test, the skin of the forearm is cleansed with alcohol and 0.1 cc. of the antigen extract injected intracutaneously to form a small wheal. At the same time, to serve as a control, 0.1 cc. of the extracting fluid is similarly injected at a suitable distance (8 to 10 cm.) from the test proper.

From a careful study of readings made at varying intervals, Bachman concludes that the resulting reactions may be read safely at 24 and 48 hours.

The procedure outlined above was followed exactly in the series reported below.

The reaction is, apparently, allergic and represents a manifestation of sensitization to trichinæ protein.

Bachman's results indicate that typical skin reactions occur within the first week of the infection and also, which is of some practical importance, that the injection may produce a local hypersensitivity which, if the test is repeated, may be responsible for a positive reaction which is never, however, as marked or clear-cut as that due to true infection.

The reactions produced in experimentally infected guinea pigs and rabbits are thus summarized by Bachman:

Plus Four. A well-defined hemorrhagic area, bluish-red in color, surrounded by well-marked hyperemia. Necrosis may or may not be present. Inflammatory edema is also quite evident varying from 0.5 to 0.6 cm. in diameter.

Plus Three. Hyperemic in type, with a well-defined inflammatory edema varying from 1 to 6 cm. in diameter.

Plus Two. An inflammatory edema varying from 1 to 6 cm. in diameter.

Plus One. A well-marked or slight edemic area varying from 1 to 3 cm. in diameter.

Of the 43 individuals concerned in the outbreak 1 died; 33 of the remaining 42 were subjected to the Bachman skin test with the results to be described.

In order to determine if there was any parallelism or proportionate relationship between the skin test and eosinophilia, as well as to detect any cases in which an original normal eosinophil count was replaced by hypereosinophilia suggestive of later dissemination of trichinæ, the original eosinophil count is contrasted with that made later at the time of the skin test and both compared with the results of the Bachman procedure.

The findings are shown in Table 1, the skin test readings being recorded in terms of the scale suggested by Bachman and above described.

If the series is considered as a whole, it will be seen that positive skin test reactions of varying degree were encountered in 18 (54 per cent) of those examined.

The true significance of the findings, however, is best made evident if the series is divided into groups, as follows:

GROUP A. Cases presenting eosinophilia when first examined together with a history of definite symptomatic manifestations of trichinosis.

TABLE 1.—ALL CASES AND CONTACTS SHOWING INCIDENCE OF SYMPTOMS AND EOSINOPHILIA.

No.	Patient.	Age.	Original eosinophil, %	Present eosinophil, %	Skin test.				Edema and hyperemia.	Ate sausage.	Sick.	Remarks.
					Control.		Test.					
					24 hrs.	48 hrs.	24 hrs.	48 hrs.				
1	G. del P.	43	32	11	0	0	0	0	0	Raw	Yes	
2	O. del P.	23	2	5	0	0	0	0	0	Cooked	No	
3	M. P.	28	10	13	0	0	±	0	Very slight	Raw	Yes	
5	Peter P.	38	23	13	0	0	±	0	Slight	Raw	Yes	
6	Patsy P.	40	10	4	0	0	±	0	Slight	Raw	Yes	Edema of legs.
7	A. P.	12	5	10	0	0	0	0	0	Raw	Yes	Slight edema of ankles.
8	R. M.	12	26	12	0	0	+2	0	5 cm.	Cooked	No	
9	Al. M.	10	21	9	0	0	+2	0	5 cm.	Raw	Yes.	
10	An. M.	14	30	21	0	0	+1	+1	0.5 cm.	Raw	Yes.	
11	E. M.	42	41	12	0	0	0	0	0	Raw	Yes	
12	Mrs. M.	42	56	24	0	0	+3	+2	7.5 cm.	Cooked	Yes	Repeatedly large amts., myalgia and some edema of legs.
13	P. F.	35	40	10	0	0	±	0	6.5 by 7.5 cm.	Raw	Yes	Sick 3 weeks.
14	J. F.	20	3	2	0	0	0	0	0	Cooked	No	
15	F. F.	3	12	5	0	0	±	±	2 by 2 cm.	Cooked	No	
16	M. F.	5	9	1	0	0	±	±	2 by 3 cm.	Cooked	No	
17	L. S.	39	2	3	0	0	+3	+1	4 by 4.5 cm.	Raw	No	Very small amount.
18	C. S.	48	1	3	0	0	+1	0	1.5 cm.	Cooked	No	
19	M. V.	43	5	22	0	0	±	0	0	Raw	Yes	Sick 5 days.
20	Mrs. V.	30	40	21	0	0	±	0	Very slight	Raw; cooked	Yes	Sick 3 weeks.
21	A. V.	2	11	2	0	0	0	0	0	Raw	No	Small amount; refused to walk for some days; "cranky and fussy."
25	B. P.	50	9	9	0	0	±	+1	See remarks	Cooked	Slight	Ate small amount; skin reaction shows small hemorrhagic center with very slight edema surrounding.
26	C. C.	30	11	17	0	0	±	±	6 by 3.5 cm.	Raw	No	Gastric distress, took purge; recently myalgia.
28	G. M.	33	11	2	0	0	0	0	0	Raw; cooked	Yes	
30	J. A.	36	0	2	0	0	0	0	0	Raw	No	Small amount.
31	G. F.	36	37	5	0	0	+1	+1	0.7 cm.	Raw	Very	
33	W. C.	10	6	9	0	0	0	0	0	Cooked	No	
34	Mrs. C.	43	0	0	0	0	0	0	0	Raw	No	Small amount.
36	A. deM.	2	2	2	0	0	0	0	0	Raw	No	Small amount.
37	Mrs. deM.	19	0	10	0	0	0	0	0	Raw	No	Small amount; recent attack of "grippe."
38	Mrs. deF.	45	0	1	0	0	0	0	0	Raw	No	Small amount.
39	M. deF.	9	1	0	0	0	0	0	0	Raw	No	
40	N. deF.	48	2	2	0	0	0	0	0	Raw	No	Small amount.
43	V. V.	4½	30	15	0	0	±	0	Very slight	Raw; cooked	Yes	

GROUP B. Cases presenting eosinophilia when first examined but without a history of definite symptomatic manifestations of trichinosis.

GROUP C. Cases without eosinophilia when first examined but developing eosinophilia later with or without symptomatic manifestations of trichinosis.

GROUP D. Cases without eosinophilia or symptomatic evidence at any time.

Group A, shown in Table 2 consisted of 12 individuals, in 9 (75 per cent) of whom the Bachman test was positive in varying degree although in 4 it was of slight intensity.

Group B, shown in Table 3, consisted of 6 individuals in 5 (83 per cent) of whom the skin test was positive.

Group C, shown in Table 4, consisted of 5 individuals, positive skin tests being encountered in 2 (40 per cent).

TABLE 2.—SHOWING INCIDENCE OF POSITIVE SKIN REACTIONS IN CASES PRESENTING EOSINOPHILIA AND SYMPTOMATIC MANIFESTATIONS WHEN FIRST EXAMINED.

Case No.	Original eosinophil count, per cent.	Skin test.		Appearance of skin.	Eosinophil count at time of skin test, per cent.
		Control.	Test.		
1	32	0	0	11
3	11	0	0	17
5	23	0	±	Very slight hyperemia	13
6	10	0	±	Very slight hyperemia	4
8	30	0	±	Very slight area of hyperemia	15
9	21	0	+ ²	Edemic and hyperemia area, 5 cm.	9
10	30	0	+ ¹	Edemic and hyperemic area, 0.5 cm.	21
11	41	0	0	12
12	56	0	+ ³	Edemic and hyperemic area, 7.5 cm.	24
13	40	0	±	Very slight area of hyperemia	21
20	40	0	+ ³	Edemic and hyperemic area, 6.5 by 7.5 cm.	10
31	37	0	+ ¹	Edemic and hyperemic area, 0.7 cm.	5

TABLE 3.—SHOWING INCIDENCE OF POSITIVE SKIN REACTIONS IN CASES WITH EOSINOPHILIA, BUT WITHOUT SYMPTOMS WHEN FIRST EXAMINED.

Case No.	Original eosinophil count, per cent.	Skin test.		Appearance of skin.	Eosinophil count at time of skin test, per cent.
		Control.	Test.		
6	10	0	±	Very slight area of hyperemia	13
8	26	0	+ ²	Edemic and hyperemic area, 5 cm.	12
16	9	0	±	Very slight area of hyperemia	9
21	11	0	0	2
23	9	0	+ ²	Edemic and hyperemic area 2 by 3 cm.	1
27	12	0	+ ²	Edemic and hyperemic area, 2 by 2 cm.	5

TABLE 4.—SHOWING INCIDENCE OF POSITIVE SKIN REACTIONS IN CASES WITHOUT EOSINOPHILIA WHEN FIRST EXAMINED BUT DEVELOPING EOSINOPHILIA LATER WITH OR WITHOUT SYMPTOMATIC MANIFESTATIONS.

Case No.	Original eosinophil count, per cent.	Later eosinophil count, per cent.	Skin test.		Remarks.
			Control.	Test.	
7	5	22	0	±	Edemic and hyperemic area, 6 by 3.5 cm.
15	5	10	0	0	
22	1	17	0	+ ³	
30	6	9	0	0	
31	0	10	0	0	

Group D, shown in Table 5 and consisting of 10 individuals, presented definitely positive skin reactions in 2 (20 per cent).

In view of the fact that eosinophilia is rather constantly associated

with trichinosis, as a rule in degree proportionate to the numerical magnitude of the larval dissemination and to the intensity of the symptomatic manifestations; and as it is a procedure always feasible and easily carried out, whereas the Bachman test requires an antigen, not easily prepared, it is both of interest and practical importance to compare the results obtained by both methods.

TABLE 5.—SHOWING INCIDENCE OF POSITIVE SKIN REACTIONS IN CASES WITHOUT EOSINOPHILIA OR SYMPTOMS.

Case No.	Original eosinophil count, per cent.	Later eosinophil count, per cent.	Skin test		Remarks.
			Control.	Test.	
17	3	2	0	0	
21	2	5	0	0	
24	2	3	0	+ ³	Edemic and hyperemic area 4 by 4.5 cm.
25	1	3	0	+ ¹	Edemic and hyperemic area, 1.5 cm.
26	2	2	0	0	
27	0	1	0	0	
28	1	0	0	0	
29	0	0	0	0	
32	2	2	0	0	
33	0	2	0	0	

The results of such a comparison are shown in Table 6 in which the eosinophil counts at both examinations are contrasted with the results of the skin test.

From Table 6 it would appear that there is in general some parallelism between the occurrence of eosinophilia and positive skin reactions. This, however, applies only to the incidence and not to the intensity of the skin reactions as it is necessary, of course, to contrast the skin reactions particularly with the eosinophils shown at the time the skin tests were made.

It is not to be expected that the two reactions should correspond exactly as they depend upon separate and differing mechanisms.

Eosinophilia in trichinosis is regarded as a reaction to the toxin liberated by the trichinæ and the assumption is corroborated by the fact that eosinophilia occurs relatively early in the disease, appears in increasing degree with the dissemination and lodgment of the larvæ in the muscles, and decreases with larval encystment, finally disappearing with larval calcification and death.

While it is true that eosinophilia is a rather frequent concomitant of allergic reactions, its rise and fall in trichinosis suggests a response to toxin rather than a manifestation of allergy.

The Bachman reaction, on the other hand, is regarded as an allergic manifestation of sensitization to the larval protein.

If this assumption is correct, it would be reasonable to expect that the allergic reaction would be not only more delicate but more constant than eosinophilia for, whereas the elaboration of toxin occurs early, reaches a peak, and later declines, sensitization to larval

protein might be expected not only to occur early but to remain as a relatively permanent factor.

TABLE 6.—SHOWING COMPARATIVE INCIDENCE OF SKIN REACTIONS AND EOSINOPHILIA.

Case No.	Original eosinophil count, per cent.	Skin test.	Eosinophil count at time of skin test, per cent.
1	32	0	11
2	2	0	5
3	10	±	13
5	23	+ ¹	13
6	10	±	4
7	5	0	10
8	26	+ ²	12
9	21	+ ²	9
10	30	+ ¹	21
11	41	0	12
12	56	+ ³	24
13	40	+ ³	10
14	3	0	2
15	12	+ ²	5
16	9	+ ²	1
17	2	+ ³	3
18	1	+ ¹	3
19	5	±	22
20	40	±	21
21	11	0	17
25	9	+ ¹	9
26	1	+ ³	17
28	11	0	2
30	0	0	2
31	37	1	5
33	6	0	9
34	0	0	0
36	2	0	2
37	0	0	10
38	0	0	1
39	1	0	0
40	2	0	2
41	30	..	15

This supposition, however, is not supported by the data presented in the table.

In Case 1, for example, while the initial eosinophilia of 40 per cent had dropped to 12 per cent at the time of the skin test, the latter was negative. In Case 7, with an eosinophil count rising from 5 to 22 per cent, the skin test was indefinite (±). In both instances the presence of eosinophilia and the history furnish indisputable evidence of the dissemination of trichina larvæ, and hence of presumable sensitization to trichina protein of which, however, evidence by means of the skin reaction was either absent or indefinite. Other illustrations of lack of correspondence are seen in the table and need not be detailed.

The particular point of the investigation was to determine, if possible, if the skin test presented any practical superiority over the demonstration of eosinophilia in the study and diagnosis of human trichinosis, which the results herewith reported do not demonstrate.

Whether or not the skin reaction may prove of practical value in veterinary medicine as a means of detecting trichinous animals remains for others to determine.

In the study of this disease in the human being the demonstration of eosinophilia furnishes a reliable and constant index of larval dissemination over which the demonstration of skin sensitivity to the larval protein appears to have no marked advantage.

The skin test also has certain technical disadvantages which do not apply to the demonstration of eosinophilia, smears for which can always be made at any time by anyone, the study of which does not require any further effort or coöperation on the part of the patient.

Summary. The results of the application of Bachman's skin test applied to 33 individuals exposed to trichinosis are reported and analyzed, from which it is concluded that in the study of human trichinosis:

1. The demonstration of eosinophilia is not only technically simpler than the demonstration of the skin test, but always feasible, whereas the skin test, requiring an antigen difficult to prepare, is feasible only when the antigen is available.

2. In point of delicacy and constancy of appearance eosinophilia serves as a reliable index of trichinosis in the human being.

3. The Bachman skin test in the study of human trichinosis presents no practical advantages over the demonstration of eosinophilia.

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THE SERUM PROTEINS IN DISEASES NOT PRIMARILY AFFECTING THE CARDIOVASCULAR SYSTEM OR KIDNEYS.

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In the course of the last 10 years, in connection with various studies that have been made in this department, a large number of serum protein determinations has been made, by methods already described, on patients without diseases of the cardiovascular or renal

systems. It seemed that analysis of these data might throw some light on the origin and functions of the protein fractions.

At present the concentrations of protein and its fractions in the serum are known to be affected by a certain limited number of physiologic variants. It is recognized that, because of their inability to traverse the normal capillary membranes, proteins are subject to fluctuations as a result of changes of hemoconcentration. If, through injury, the impermeability of the capillary walls becomes impaired so that protein seeps into the interstitial fluids, the serum proteins will fall.^{7 8 21} Fluctuations due to these causes may attain considerable magnitude, but are of necessity self-limited and transitory. In alterations of protein concentration resulting from changes of hemoconcentration both protein fractions are equally affected; while in those referable to changes of vascular permeability, albumin, because of its smaller molecular size, should suffer most.

When serum protein as such is lost from the body in the urine or in exudates, or is withdrawn by plasmapheresis, the total protein concentration falls. Regeneration is, however, effected with extreme rapidity unless drainage of the serum is constantly maintained or is repeated at intervals.^{5 40 66 68 76} There is no complete unanimity of opinion concerning the relative rates of regeneration of the two protein fractions, possibly because uniform experimental conditions have not been maintained by all observers. Proteinuria leads especially to albumin depletion because this is the protein fraction which is chiefly lost, probably on account of its smaller molecular size.

Malnutrition, or more exactly, protein starvation, results in hypoproteinemia in which, again, albumin is chiefly affected.^{9 10 28 34 37 42 43 64 74 75} The serum protein depletion, like the body protein loss from which it arises, can be retarded and mitigated by the administration of large quantities of fat and carbohydrate; however, regeneration of the serum proteins can be accomplished only when enough protein is added to the diet to permit restoration of the previously wasted body protein.^{19 28 42 43 74} It would seem quite possible under these circumstances for both body protein depletion and hypoproteinemia to coexist with obesity in subjects who had undergone wasting with an inadequate protein intake, either for therapeutic purposes or in the course of disease.⁵³

Whether circulating proteins have a direct nutritive function and can be utilized by the cells, is uncertain; but the recognized impermeability of the cell membrane to protein renders it extremely unlikely.

Increases of serum globulin are encountered in a variety of infectious diseases.^{2 14 29 37 44 45 56 63 65 67 71 73 77 78} This and the close association of certain antibodies with particular globulin fractions has given rise to much speculation concerning the relation of this fraction to immune reactions. In certain types of infections,

especially syphilis,^{56 71 78} kala azar^{44 67 78} and schistosomiasis japonica⁴⁷ hyperglobulinemia may attain extreme limits. Increases are further reported to accompany carcinoma.^{20 32} In some cases of myelomatosis extraordinarily high figures have been reported.^{4 25 30 52} In cirrhosis and certain other diseases of the liver high globulin is also frequently encountered.^{1 57 71 77} Hypotheses concerning the origin of globulin have been developed on the basis of these pathologic disturbances.

The function of the serum proteins which will be the chief concern of this paper is the protein osmotic pressure and its relation to the theory of transudation and edema formation proposed by Starling⁶⁹ which postulates that the interchange of fluid between the blood and the tissues (or interstitial fluids) is determined by the balance between the hydrostatic force of the capillary blood pressure, favoring transudation, and the osmotic pressure of the plasma colloids, especially the proteins, which tends to prevent passage of fluid out of the blood in the capillaries and to draw it into the blood from the interstitial spaces. The theory has received strong support from experimental study and from clinical investigations of nephritis, in which a close correlation between edema formation and serum albumin concentration has been demonstrated.^{13 15 50 51 54 61} On the other hand, objections have been raised to the theory on the ground that the correlation between edema and the serum protein or serum albumin level in conditions other than nephritis is less satisfactory and because in certain cases of nephritis alterations of proteins or of water balance occur independently of one another.^{11 16 37} It must be recognized, however, that this theory does not postulate exact correlation between serum colloid osmotic pressure and transudation, but a reversible equilibrium reaction in which the balance of the fluid exchange between blood and tissues is determined by the relative magnitudes of hydrostatic and colloid osmotic pressures. In measurements of this equilibrium, attention has been focussed upon colloid osmotic pressure because it is susceptible to accurate estimation and is relatively uniform throughout the body. Even if the capillary blood pressure could be measured with equal facility and accuracy in any single capillary bed, no inferences could be made from such measurements concerning capillary pressure in general, because of the unpredictable differences and fluctuations of capillary pressure in various organs and tissues of the body. Even if the balance of hydrostatic and colloid osmotic forces favors transudation, edema does not necessarily result, because reabsorption into the blood stream is not the only channel for escape of interstitial fluid; it may return to the blood through the lymph; nor, once started, does the process of transudation progress indefinitely. Weech⁷⁶ found that in both plasmapheresis and protein starvation the shift of fluid to the tissues increased gradually as the proteins fell and that the appearance of frank edema only marked

the point where the accumulation of fluid in the interstitial spaces became obvious to the physical senses of the observer. Presumably, lymph flow is augmented by passage of fluid from the bloodvessels. Landis and Gibson³⁹ demonstrated that the volume of fluid which could be driven into the tissues of a limb by obstructing the venous return was self-limited and varied with the capillary pressure produced. The limiting factor in this case may be the elasticity or resistance to expansion of the tissues themselves, which may also be instrumental under other circumstances in accelerating lymphatic drainage. Weech, Snelling and Goettsch⁷⁶ found that in malnutrition, edema appeared before the serum proteins had fallen to a level low enough to yield edema after plasmapheresis. He drew the reasonable inference that the inelastic subcutaneous tissues of the malnutrition victim offered less resistance to expansion by fluid than the well-preserved firm tissues of the plasmapheresis animals. Finally alterations of vascular permeability must be taken into consideration and it must be appreciated that they may result from mere changes of vascular tone as well as from actual injury of the capillary walls. Their effect is not to accelerate leakage of water from the vessels directly (this may equally well take place in both directions); but to allow colloids to escape and thus to reduce the effective colloid osmotic pressure in the blood stream, which is determined not by the concentration of colloids in the plasma but by the difference between the colloid concentration in the plasma and that in the interstitial fluids surrounding the capillaries.

The forces controlling the passage of fluid between capillaries and tissues are, then:

<i>Favoring transudation.</i>	<i>Opposing transudation.</i>
Capillary blood pressure.	Tissue resistance.
Colloid osmotic pressure of interstitial fluids.	Colloid osmotic pressure of plasma.

In addition one must recognize that the extent of fluid accumulation and the collection of edema are probably influenced by tissue resistance and the rate of lymph drainage. The recognition of the influence of these additional forces in no way violates the principles of Starling's theory.

The exact purpose of the present analysis might best be defined: (1) as an attempt to learn how far the abnormalities of serum proteins in a variety of diseases can be attributed to the general physiologic influences mentioned above, and to what extent they must be ascribed to specific disturbances referable to the particular diseases under consideration; (2) to study the relation of edema to serum protein concentrations in order to determine how far its appearance in non-renal diseases is compatible with the Starling theory.

In this analysis the results of certain studies on individual sub-

jects are used for more than one purpose. For example, among the diabetics were subjects suffering from carcinoma, tuberculosis, anemia, liver diseases and a variety of other disorders. Other instances of overlapping are common. It is obvious that determinations on such patients cannot be relegated arbitrarily to a single category, but must be analyzed in the light of every disorder which the subjects exhibited. Altogether, the data under consideration included 542 determinations of total proteins from 374 patients,

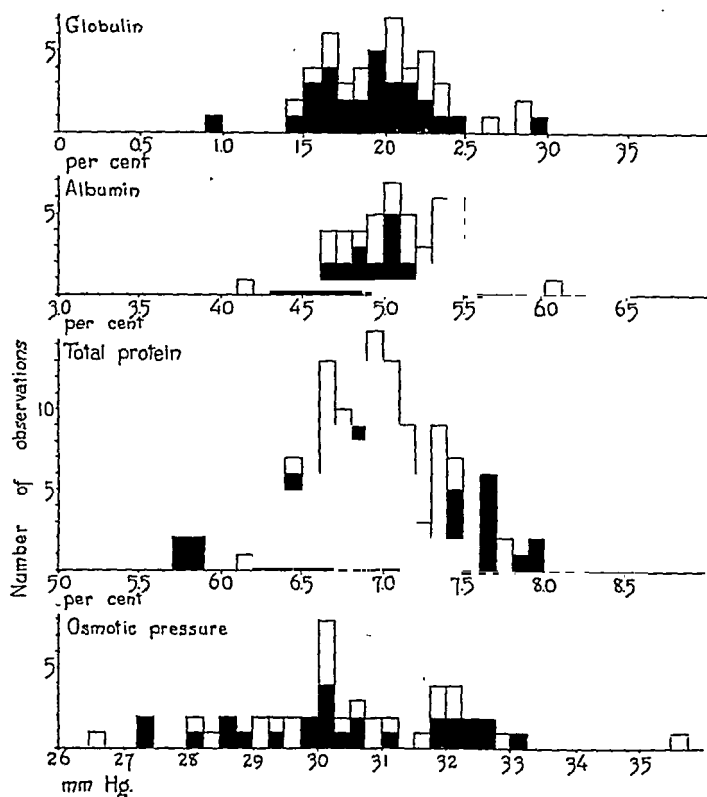


FIG. 1.—The proteins of the serum of normal adults. Solid squares represent males; open squares females.

with 332 determinations of protein fractions from 215 patients. From this list are excluded all patients with nephritis, uncomplicated heart disease and diabetes with acidosis.

The Concentration of Proteins in the Serum of Normal Persons. Before proceeding to the examination of the data from patients it may be well to define the limits of variation in normal human subjects as accurately as possible. Figure 1 shows the concentrations of protein and protein fractions found in the serum of normal individuals (physicians, nurses, medical students and laboratory workers) in this laboratory. Analyses were made by the modification of the

method of Howe described by Bruckman, D'Esopo and Peters.⁹ The 109 total protein determinations from 52 individuals fall between the limits of 5.7 and 8 per cent. All but 4 are above 6.1 per cent and 90 per cent lie between 6.3 and 7.7. All the individuals who had proteins below 6 per cent, on other occasions had higher concentrations. Fifty albumin determinations from 34 subjects varied from 4.1 to 6.1 per cent. Of these only 1 lay above 5.5 per cent. Globulin varied from 0.9 to 3 per cent with only 1 analysis below 1.4 per cent. The 4 values above 2.5 per cent are, furthermore, scattered. It would seem justifiable from these data to accept as the limits of normal variation for total protein 6 to 8 per cent, for albumin 4 to 5.5 per cent, and for globulin 1.4 to 3 per cent. Perhaps the upper limit for globulin should be set at 2.5 per cent. This fraction is so largely influenced by inflammatory processes that it is not improbable that the scattered values above this point represent effects of mild infections, especially of the respiratory tract. This impression is supported by the fact that the high values were all secured in the months of December, January and February. Moreover, there is a distinct suggestion in Figure 2 that in the winter

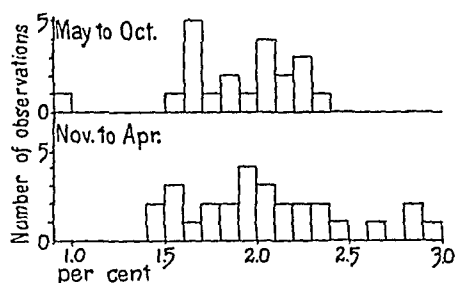


FIG. 2.—Seasonal variations of normal serum proteins.

months high values are more common. In the months of November to April, inclusive, in 7 out of 28 observations globulin exceeded 2.3 per cent, whereas in the remaining 6 months only 1 of 21 lay above this point and this subject is known to have had a severe cold at the time the blood was analyzed. It would seem likely, then, that the range of variation of globulin in absolutely healthy subjects is more restricted than the limits set above. However, considering the prevalence of mild respiratory infections in this climate it is hardly safe to attach any especial importance to globulin values between the limits which have been mentioned, 1.4 to 3 per cent. These limits are in general agreement with those which have been found by other observers who have employed acceptable methods.^{13 26 35 37 41 77} Starlinger and his associates⁷¹ give somewhat higher globulin and lower albumin figures. However, their subjects were not in the strictest sense normal, but patients suffering from minor conditions which they believed would have little effect on serum proteins. As the commonest serum protein disturbances

encountered in pathologic conditions are increase of globulin and decrease of albumin their values should be expected to differ, as they do, from those of other observers.

In an earlier paper⁹ it was suggested that total protein and globulin were usually higher in females than males. With the collection of further analyses this sex distinction is no longer apparent. It seems likely that the erroneous impression was referable to the seasonal effect noted above, the earlier studies on women having been made chiefly in the winter months.

In man^{3 48} as well as in other animals¹² it has been found that the concentrations of total protein and the protein fractions, especially globulin, are lower at birth than in adult life. The degree of reduction and the rate of increase with growth have been imperfectly defined. Although the present paper deals almost entirely with data secured from adults and adolescents, for the sake of other observers it may be useful to add certain determinations on infants which have been made available through the kindness of Dr. Dan C. Darrow, in whose laboratory they were made.

Age.	Number of observations.	Total protein, per cent.	Albumin, per cent.	Globulin, per cent.
Premature	26	4.94 \pm 0.59	3.58 \pm 0.46	1.18 \pm 0.71
First 2 weeks . . .	20	5.52 \pm 0.58	3.73 \pm 0.31	1.78 \pm 0.45
5 to 8 months . . .	14	6.29 \pm 0.33	4.28 \pm 0.38	2.01 \pm 0.34

These figures do not give a complete picture of the curve of protein development. They do indicate that as early as the middle of the first year of life the total proteins and fractions have risen into the lower limits of the range of adult values.

Although direct determinations of protein osmotic pressure have not been included in this study, they have been estimated whenever fractions were determined by the factors of Govaerts²² who has estimated that albumin exerts an osmotic pressure of 5.5 mm. Hg and globulin 1.4 mm. Hg for every per cent of protein in normal serum. By direct measurements the colloid osmotic pressure of the serum of normal adults has been found to vary between 20 and 32 mm. Hg.^{13 15 26 31 38 61} Although the estimated values given for normals in Figure 1 have no absolute value, they fall within the usually recognized range and may serve for comparative purposes. According to these the lower limit is 26 mm. Hg, with the great majority above 28 mm. Hg. When serum is diluted the colloid osmotic pressure falls more rapidly than the serum proteins, *i. e.*, the specific osmotic pressure of the proteins diminishes.^{18 31 36 46 72} For this reason when proteins are low, as they are in many of the pathologic cases, the values given for osmotic pressure are too high. However, because they serve to indicate relative values no attempt has been made to correct them by the formulæ proposed by Verney,⁷² Fishberg¹⁸ and others.

Diabetes. The relation of hypoproteinemia to malnutrition in diabetes, as well as the hyperproteinemia that accompanies the hemoconcentration of diabetic acidosis, has been discussed in previous papers from this department.^{9 55} Since the earlier of these articles, however, a far larger body of data has been collected. This is presented in Figure 3. None of the cases included in this series had acidosis or had recently suffered from it, although, as is usual in hospital cases, almost all had some complication which had temporarily, at least, aggravated their diabetic conditions. Total

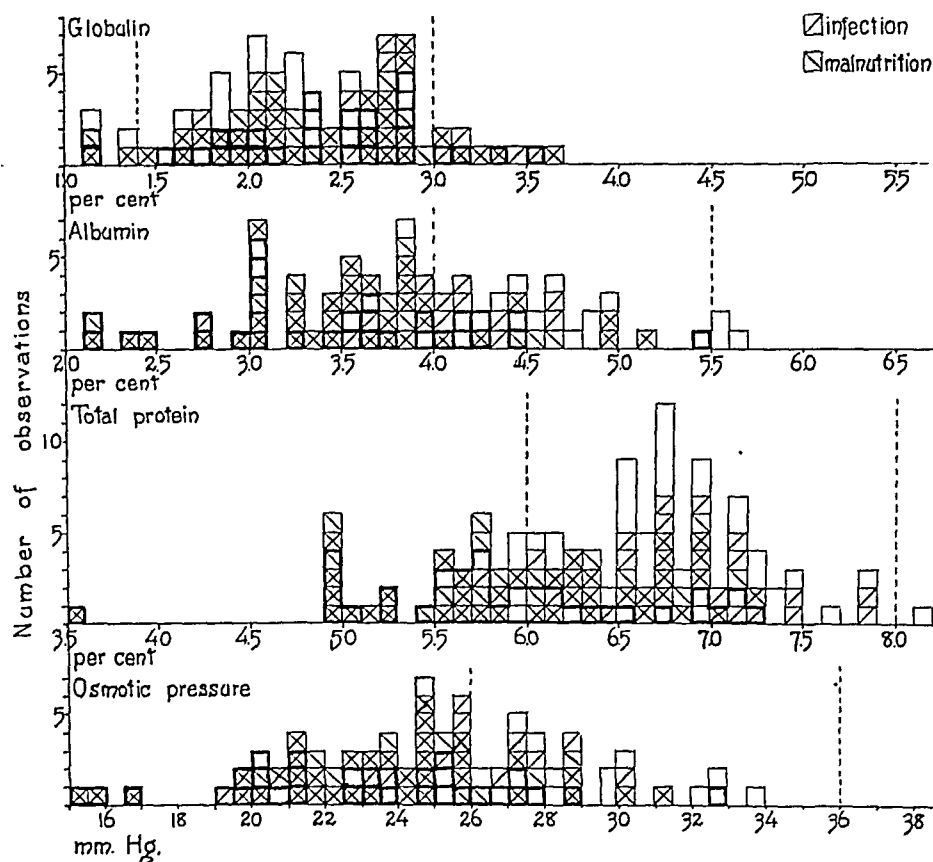


FIG. 3.—The serum proteins of patients with diabetes. Heavily outlined squares indicate the presence of edema. Normal limits of variation are marked by the broken vertical lines.

proteins were determined 117 times in 78 patients, fractions 78 times in 50 patients. Total proteins were low 34 times, high only once. This last patient was well nourished, and had a mild diabetes complicated by an ulcer of the foot. Unfortunately, his protein fractions were not determined.

Of the 34 low proteins, all but 7 occurred in patients who were obviously malnourished. Of these 7, 2 can be dismissed briefly. Although the total proteins were only 5.73 and 5.93 per cent respectively, albumin was 4.19 and 4.20, within normal limits; the hypoproteinemia resulted from the fact that globulin was 1.54 and 1.73,

at the lower limit of normal. Total proteins of 4.95 per cent were found in an obese old woman, suffering from obstruction of the common bile duct. She had been admitted the night before, after 3 days of increasing jaundice and continued vomiting, dehydrated and in shock, with proteins 6.05 per cent. The second determination was made the following morning after she had received large amounts of fluid subcutaneously and intravenously, but still remained in the condition of surgical shock. The 3 days of starvation may have played some part in the protein reduction; but it is more probable that this was referable chiefly to the state of shock. In this condition it has been demonstrated that the vessels permit the escape of protein from the blood stream^{7 8 21} and that intravenous administration of fluids, if it does not overcome the shock, only washes the proteins out more rapidly.^{7 8} Two other patients with proteins of 5.98 and 5.96, just below the normal limits, although not strictly malnourished, had lost considerable weight.

The remaining two deserve especial consideration. Both, though distinctly obese, had suffered from serious infections, associated with anorexia and nausea which had, for long periods, forced them to subsist on diets far below maintenance standards. One was convalescing from a protracted bronchopneumonia; the other, in addition to arteriosclerotic heart disease with congestive heart failure, had pneumonia and empyema. Both had subsisted for long periods on diets extremely low in proteins and calories and, in view of their infections, there can be little doubt that they had wasted large amounts of body proteins. The question of malnutrition under such conditions becomes one of definition. Evidence points to the fact that the serum albumin reduction of malnutrition is referable to protein wastage, which these patients undoubtedly had. It is conceivable that subjects possessing unusually large stores of fat, if deprived of protein and given insufficient calories, especially if they were subjected to an infection which caused specific protein destruction, might deplete their body proteins more rapidly than their excess fat stores. In this case malnutrition, if defined as a state in which body protein is depleted, could coexist with obesity.

Albumin was abnormally low 45 times, high only twice. The last two were 5.59 and 5.65, just above the upper normal limit. Of the low values only 6 were observed in patients without obvious malnutrition. Of these 3 have been mentioned among the patients with low proteins with malnutrition: the patient with biliary cirrhosis and the 2 obese patients who had wasted because of infections and anorexia. Three more obese subjects of the same kind had low albumin. One had congestive failure and an ulcer of the toe; the second heart failure and bronchopneumonia. The third, admitted because of a coronary occlusion, although still decidedly obese, had recently lost 40 pounds of weight.

The rise of serum albumin with improvement of nutrition was

demonstrated in an earlier article. Essentially similar results have been found in additional cases, as well as a steady fall of albumin in patients with continuous wasting. Before it is possible to conclude that malnutrition is alone responsible for albumin reductions, it must be shown that patients with high albumin are free from malnutrition. This point is more difficult to establish for several reasons, especially in diabetes. In 9 of the 31 instances in which albumin was normal or above normal, some degree of malnutrition was mentioned in the case records. One of these subjects, with albumin 4.46 per cent, a fractured femur and pleurisy with effusion, was thin and had lost considerable weight in the course of the preceding 10 years, during which he had been treated for diabetes; but had good musculature and firm, elastic skin and subcutaneous tissues. His diabetes had been well controlled, for a few days immediately following his fracture, and he had eaten sufficient food until the development of a pleural effusion about 3 days before the blood examination. His condition seemed to be one of leanness rather than malnutrition and serves to illustrate again the difficulty of evaluating the nutritive state. Another of the group, with pulmonary tuberculosis and serum albumin 5.19, was obviously emaciated. However, he had already improved greatly under treatment and gained 6 pounds. In our own work,⁹ as in the studies of famine edema made by Weech and Ling,^{42 75} it has been noted that, with improvement in nutrition, serum albumin rises more rapidly than body weight, and may reach the normal level while there is still evident emaciation. Two other subjects with albumin 4.02 and 4.67 respectively were dehydrated, the former, with advanced tuberculosis, by reason of anorexia and vomiting which prevented him from taking fluids, the other because of diarrhea. Two patients, one with a gluteal abscess and high fever, the other with hyperthyroidism and cystitis, had considerable glycosuria at the time of the blood examinations. In these, also, dehydration and attendant hemoconcentration may have been responsible for the high albumin values. Although it is possible by such reasoning to explain the exceptions to the general rule that albumin falls with malnutrition (body protein wastage), it is difficult to escape the appearance of arguing purposefully. The possibility cannot be excluded that other influences which tend to increase albumin may in some of these cases have been sufficiently active to overcome the effects of protein starvation. As albumin concentrations are closely related to the nutritive state in the great majority of diabetics, this influence is probably not connected directly with diabetes. The complications from which the malnourished patients with high albumin suffered are so various that no common factor can be found among them.

In contradistinction to the protein and albumin values, those for globulin are chiefly within normal limits. Four are abnormally low. One of these patients had a secondary anemia of unknown origin,

a second seemed to be suffering from nothing but a psychoneurotic condition. The remaining 2 had severe infections of the extremities with malnutrition. One had in addition massive edema and profuse albuminuria. There seems to be nothing to which the reductions of globulin can be definitely ascribed. It is of more than passing interest that the group should include 2 instances of severe infection, in view of the general tendency, mentioned above, for infections to be accompanied by high globulin. In this connection only one thing stands out clearly: although infections were seen at all globulin levels, globulin above the normal limits was observed only in the presence of infections. This suggests that infections increase globulin. It is impossible from these few observations to say whether this is true of only certain types of infections or whether other factors of an unknown nature have, in the exceptions to the general rule, prevented the usual globulin increases.

It remains to examine the relation between serum proteins and the incidence of edema. In this connection Fig. 3 leaves no doubt that globulin can be summarily dismissed. Edema is seen with equal frequency at all globulin levels. With albumin below 3.1 per cent, edema was lacking only once—in a malnourished patient with acute arthritis of the knee and glycosuria. Whether glycosuria or fever may have caused him to excrete fluid despite the low albumin is subject for conjecture only. As albumin increases from 3.1 to the lower normal limit, 4, edema occurs with diminishing frequency and only in the presence of some other factor which aggravates the tendency to transudation. In 8 of the 9 instances in which edema was observed with albumin between 3.2 and 4 per cent, there was associated arteriosclerotic heart disease with congestive heart failure. Direct evidence of the cardiac origin of the edema was secured in many of these cases by the ready response to digitalis. One patient, with proteins of 3.69, ascites and moderate edema of the lower extremities was suffering from cirrhosis. The two remaining observations were made on a boy without obvious complication other than malnutrition, who, having been urged to drink large amounts of fluid, voluntarily took from 4 to 6 liters of fluid a day, chiefly in the form of broth containing 1 per cent of NaCl. Although earlier with albumin 3.82 he had been free from edema, under this régime he gained 9 pounds in 11 days, in spite of the fact that, with improved nutrition, the albumin had risen to 3.95 per cent. This seems to be an illustration of the well-recognized fact that by a high salt and fluid intake edema can be produced at a protein level higher than that at which it is likely to occur spontaneously.

Of the 8 instances in which edema was found with normal serum albumin 4 occurred in patients with arteriosclerotic heart disease and congestive failure. In a patient with hyperthyroidism the edema may also have been referable to heart failure. The other

3 are not so easily explained. One subject with advanced pulmonary tuberculosis and extreme emaciation had become dehydrated from inability to take fluids; another had a gluteal abscess which had been attended by high fever for a long period; the third was suffering from a severe secondary anemia of unknown origin. It is quite possible that these conditions may have given rise to circulatory insufficiency, although there were no frank signs of heart failure. However, it may be just as well to admit that the edema in these cases is inexplicable. After all, considering the difficulties of evaluating the circulatory state, it is not surprising that in 3 instances out of 78 the findings should not conform exactly to the Starling theory.

Concerning the total proteins little need be said. The relation of edema and malnutrition to total protein is less definite than that to albumin because of the frequent coincidence of low albumin and high globulin. For the same reason protein is less often deficient than albumin.

Strictly speaking, neither albumin nor globulin alone should be related to edema, but rather the colloid osmotic pressure of the serum, which is the sum of the effects of two fractions. The correlation between edema and estimated osmotic pressure is quite definite, with the same exceptions which were noted in the discussion of albumin figures above. However, it is not notably better than the correlation with albumin. The reason for this presumably lies in the fact that the specific osmotic pressure of albumin is 4 times as great as that of globulin. Therefore, only extreme changes of globulin have any considerable influence upon osmotic pressure.

On the whole, then, there is little or nothing to indicate that diabetes *per se* has any effect upon the concentrations of protein and protein fractions in the serum. Dehydration may raise both fractions. Reduction of protein and albumin can be traced almost invariably to malnutrition, increases of globulin, to the influence of infections. It should be mentioned that albuminuria of serious degree was present in only 5 instances and therefore can have played no part in the production of albumin deficiencies in the great majority of cases. The appearance of edema, finally, in 75 out of 78 observations, followed the predictions of the Starling theory inasmuch as it occurred only when the values for serum albumin and colloid osmotic pressure were reduced considerably below the normal limits, unless there was some complication which would tend to increase capillary pressure.

Neoplasms. Total proteins were determined 65 times in 47 patients and protein fractions 51 times in 35 patients afflicted with various neoplasms, mostly malignant (Fig. 4). The statements of Galehr²⁰ and Kennaway³² that globulin is usually increased in carcinoma is hardly substantiated by these data. There are, to be sure, no abnormally low values and there is a considerable number of very high values; but of the latter all but one occurred

in 2 cases of general myelomatosis, the other in a patient with hypernephroma. Of the 3 values slightly above normal (between 3 and 3.5), one was from a patient with carcinoma of the breast with extensive metastases; the other 2 were found in dehydrated subjects (1 with carcinoma of the stomach and pyloric obstruction, the other with diabetes insipidus), and may have been referable only to hemoconcentration. Furthermore, 6 of the 14 observations in which globulin was in the upper normal range were made on patients with carcinoma of the gastro-intestinal tract with obstruction and dehydration. Many other patients in the lower ranges had similar conditions. If, then, due account is taken of the effects of hemo-

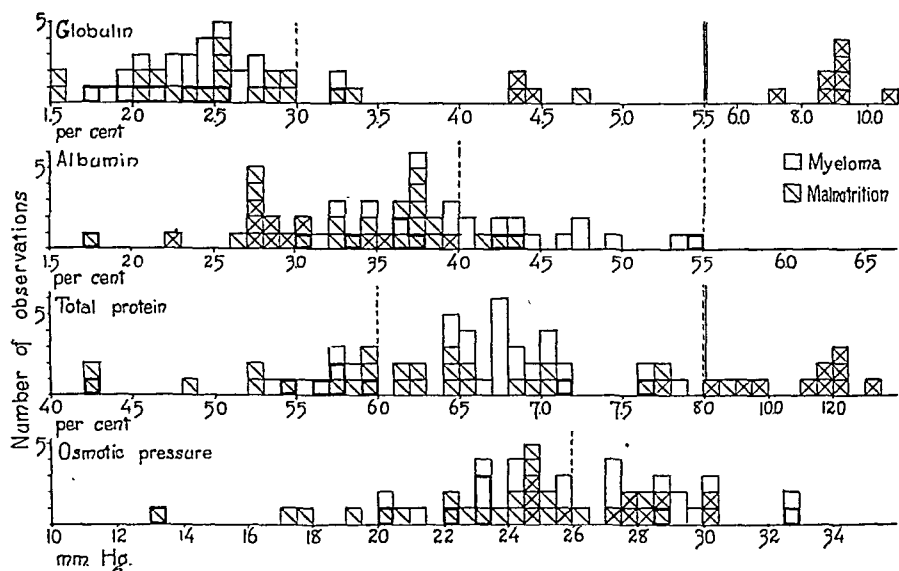


FIG. 4.—The serum proteins of patients with neoplasms. Heavily outlined squares indicate the presence of edema. Limits of normal variation are marked by the broken vertical lines. The globulin and total protein scales, above 5.5 and 8 per cent respectively, are reduced to permit inclusion of the myeloma case.

concentration, the tendency to hyperglobulinemia in carcinoma is even less evident than the figure would indicate. In fact, excessive serum globulin seems to attend especial types of tumors rather than carcinoma in general.

Extremely high serum globulin values have been reported in myelomatosis by Bannick and Greene,⁴ Kumpf,³⁷ Perlzweig, Del Rue and Geschickter,⁵² Jores,³⁰ and others, which has given rise to theorizing about the origin of both Bence-Jones protein and serum globulin. The fact that, of the only other 2 patients with high globulin not referable to hemoconcentration, one had extensive bone metastases and the other hypernephroma which so commonly metastasizes to bone, suggests something more than a casual relation between

the site of these tumors in the bone marrow and the globulin increases. On the other hand, this series contains several other bone tumors, both primary and secondary, with normal globulin. Moreover, normal,^{4 24 25} indeed even low,²⁵ serum globulin has been reported in cases of true myeloma. At present, then, it is impossible to do more than recognize the association of hyperglobulinemia with certain cases of myelomatosis as an aid in diagnosis. The patient in Fig. 4 with the highest globulin excreted no Bence-Jones protein. The general rarefaction of the bones with hypercalcemia had led to the diagnosis of hyperparathyroidism. The presence of a high color index anemia which did not respond to therapy together with the high serum globulin gave a clue to the proper diagnosis, which was verified at autopsy. It may be added that the most painstaking search revealed no adenoma nor hyperplasia of the parathyroid glands.

Low serum albumin is common,^{6 37} but, as in diabetes, is rarely found without obvious malnutrition, in this series only 6 times out of 36. Three of these were in obese patients who had recently lost much weight: the first had melanotic sarcoma with extensive metastases; the second, a tumor of the right kidney, jaundice and extreme anorexia; the third, a carcinoma of the breast and extensive bone metastases. Two were from a patient with syphilitic heart disease, congestive heart failure and carcinoma of the prostate with metastases to the lungs, who was still apparently well nourished but had also lost weight. The remaining patient had pernicious anemia as well as prostatic carcinoma. With the possible exception of this last case there is nothing to suggest that the albumin reductions need be attributed to any effects of carcinoma other than its influence on nutrition. On 3 occasions albumin was normal in the presence of obvious malnutrition. All these subjects were distinctly dehydrated: one with carcinoma of the pancreas, one with carcinoma of the esophagus, and the third by a diabetes insipidus.

It is surprising to find edema in only 1 of 11 instances when albumin lay below 3 per cent. The reasons are not hard to find. Three of the other observations were made on patients with complete pyloric obstruction and extreme dehydration. The remainder are from one of the patients with myeloma. In this case, although albumin was reduced to the level at which edema would ordinarily be expected, globulin was so greatly elevated that the colloid osmotic pressure, as can be seen at the bottom of the figure, was within normal limits. Edema occurred with normal albumin only twice, in patients with obvious heart failure; and, with albumin between 3.5 and 4, once in association with pernicious anemia, once in the presence of heart failure, and once in a patient with suppression of urine who had received large quantities of saline subcutaneously.

The total protein figures are chiefly valuable in illustrating the lack of correlation between total protein values and the nutritive

state in conditions in which, for some reason, globulin is elevated. The colloid osmotic pressure figures, as has been mentioned, explain the absence of edema in the malnourished myeloma case with low serum albumin. Again the absence of edema at low osmotic pressures is referable to dehydration in patients with vomiting due to carcinoma of the gastro-intestinal tract.

The results in general lend little support to the views that malignant tumors have any consistent effect on serum protein or its fractions, with the single exception of the globulin increases found with certain peculiar neoplasms, and especially myelomatosis. The theory of Starling adequately explains the incidence of edema.

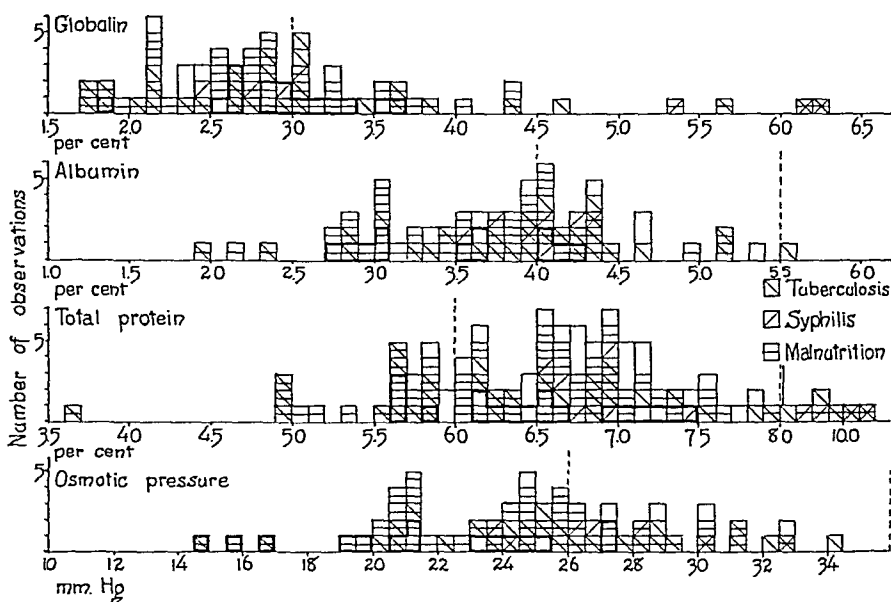


FIG. 5.—The serum proteins of patients with infections. Heavily outlined squares indicate the presence of edema. Limits of normal variation are marked by the broken vertical lines. The total protein scale is reduced above 8 per cent.

Infections. In various kinds of infections total proteins were determined 102 times in 83 subjects, protein fractions 62 times in 50 subjects (Fig. 5). Although globulin is never low and frequently exceedingly high, a large proportion of the determinations lie within normal limits. Because the actual purpose of the investigation was to secure data from patients with high albumin and low globulin, undue emphasis has been laid upon tuberculosis and syphilis, which make up more than half the observations.

In the latter disease especially high values (the 3 above 5 per cent) were found in a patient with extreme gummatous ulceration of the pharynx together with pulmonary tuberculosis and in a patient with congenital syphilis involving the liver, bones and central

nervous system. The other high value, 3.04, was from another subject with syphilitic ulceration of the pharynx. In the few other cases with non-ulcerative lesions and in a group with syphilitic aortitis and heart failure not included in this series, globulin was normal. Among the tuberculous the highest globulins were found in the case mentioned above who also had syphilis; a value of 5.67 in a patient with a lesion of the thoracic vertebræ and a cold abscess; 4.69 in a patient with extensive pulmonary cavitation. With 3 exceptions the remainder were associated with advanced ulcerative lesions of one kind or another. Of the 3 exceptions 2 had pleurisy with effusion and the third an acute tuberculous pericarditis. Among those with miscellaneous infections, globulin above the normal limits was observed only in patients with frankly suppurative or ulcerative lesions; twice with empyema, 3 times with gangrenous ulcerations of the lower extremities, once in a boy with a long-standing gluteal abscess. To these might possibly be added 2 patients with ulcerative colitis, but their marked dehydration may have been responsible. With the limitation admitted above, they suggest that the most striking globulin increases result from chronic suppurative infections. Only to this extent do they seem to have the evil prognostic significance which has been attributed to them by certain observers.^{2 27} Hyperglobulinemia also seems to be especially characteristic of certain specific types of infections,^{47 67 78} among which ulcerative tuberculosis and syphilis must be ranked.^{2 78}

Reduction of albumin appears to be a far less consistent effect of infections than the literature would lead one to believe and, when it does occur, seems to be almost invariably associated with malnutrition. Malnutrition is, however, found with surprising frequency without any reduction of albumin, although it becomes less common as albumin increases. The definition of malnutrition is extremely difficult in the diseases under consideration. Often determinations were made at a time when emaciation was still extreme, but appetite had returned and restoration of tissues had already begun. For example, one case who is marked as malnourished was convalescing from typhoid fever. With a normal temperature she was eating 3500 calories daily. Her serum albumin, which during the active stage of the disease had been 2.78 per cent, had risen to 4.01 per cent. Similar cases are common and add to the impression that the serum albumin in malnutrition returns to the normal level before tissue proteins have been completely restored. In other cases, too numerous to catalog in detail, fever, diarrhea, vomiting or other symptoms have caused dehydration and hemoconcentration.

Edema is found in more than half the cases with serum albumin below 3.1 per cent and invariably when the colloid osmotic pressure is less than 20 mm. Hg. Again the complexity of the clinical conditions renders exact analysis of the low albumin cases without

edema and the high albumin cases with edema difficult. In the majority of instances, however, the factors which have been mentioned in analyses of diabetic and tumor cases, especially dehydration and circulatory failure seem to afford adequate explanations for the exceptions to the general rules connecting edema with serum albumin.

The fallacy of attempting to correlate functional disturbances with total protein concentrations is well illustrated in some of the cases with high globulin and low albumin, yielding normal or high total protein values.

Although the miscellaneous nature of the data is confusing, the general impression which they yield is that infections of certain types evoke an overproduction of globulin or at least a greater mobilization of globulin into the blood stream. Albumin suffers depletion only if there is malnutrition. Edema develops if the colloid osmotic pressure falls below a certain point if the water stores of the body are not depleted by diarrhea, vomiting or other dehydrating influences. It may also be precipitated by circulatory failure or stasis. In this connection one case deserves especial mention. The patient with pulmonary, intestinal and vertebral tuberculosis had massive edema below the waist and serum albumin of 2.87 per cent. Somewhat later albumin rose to 3.66, but the edema remained unchanged. At autopsy he was found to have partial obstruction of the vena cava. Ito, Seki and Nakazawa²⁷ have ascribed the albumin deficiency to leakage of proteins through damaged capillaries. If such hypothetical leakage does occur, it must be self-limited because the proteins will presumably find their way back to the blood stream through the lymph. Moreover, if such seepage were great the colloid osmotic pressure of the interstitial fluids should rise to such an extent that edema would develop at relatively high protein levels. Of this there is no evidence in the figure.

Anemia. The results of examinations of patients with anemia are presented in Fig. 6. Anemia is here defined as a condition in which hemoglobin is less than 70 per cent, or oxygen capacity less than the corresponding concentration, 14.6 vols. per cent. All but 8 of the determinations of fractions (from 6 cases) and all but 21 of the total protein determinations (from 15 cases) are included under other categories in other figures. The figure does not give an accurate picture of the serum protein concentrations in anemia because the data were not collected primarily for this purpose. The cases were selected chiefly to investigate the causes of edema and the effects of malnutrition. There are, however, enough adventitious observations to make it extremely doubtful whether anemia, either primary or secondary, is attended by any consistent alteration of the concentration of protein or its fractions.

The cases with high globulin are chiefly represented by those with

infections or neoplasms which have already been mentioned (the myeloma cases should properly be included, but have been omitted). Low globulin was seen in one case with profound pernicious anemia. Albumin is frequently reduced, but seldom when there are not frank signs of malnutrition. The occurrence of malnutrition with normal albumin values may, as in infections, indicate chiefly the impossibility of estimating or defining this condition.

Perhaps the most striking difference between this figure and previous ones is the greater frequency of edema at low albumin levels and the apparently higher level at which the line between edematous and non-edematous patients is drawn. In point of fact in only 4 instances was edema absent when albumin was below 3.9 per cent,

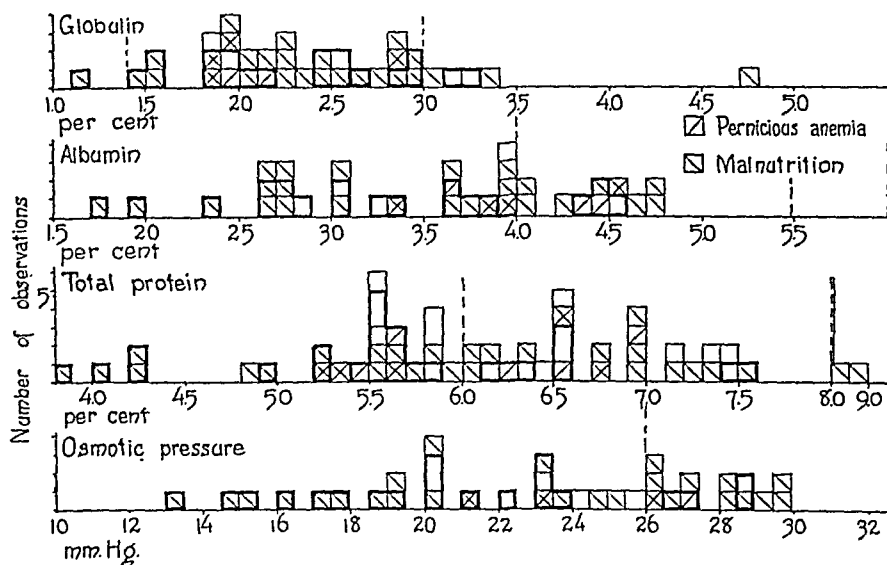


FIG. 6.—The serum proteins of patients with anemia. Heavily outlined squares indicate the presence of edema. Limits of normal variation are marked by the broken vertical lines. The total protein scale is reduced above 8 per cent.

whereas in the other conditions a sharper line of demarcation has been about 0.8 per cent lower. Of the 4 exceptions 2 had carcinoma of the stomach and were dehydrated from vomiting; 1 had acute arthritis and diabetes with fever and glycosuria; the 4th, with an albumin of only 3.63 had 4.75 per cent of globulin, bringing the estimated colloid osmotic pressure to 26.7, within normal limits. The line for edema appearance in the colloid osmotic pressure section of the figure is drawn quite as sharply at 24 mm. Hg. In the total protein section the line is again drawn rather definitely at 5.8 per cent, just below the normal limits of variation.

All these facts would suggest that possibly some characteristic of the condition of anemia itself tends to facilitate the appearance of edema. This impression is strengthened by the fact that edema was found in 4 instances when albumin was above 4 per cent and

colloid osmotic pressure greater than 26 mm. Hg, the lower limits of normal variation, in only one of which was it associated with obvious heart failure, venous obstruction or other circulatory disturbances. This greater tendency to edema in anemia may be due to alteration of capillary pressure or to increased capillary permeability resulting from less perfect oxygenation. Schade and Claussen⁶² found in their model capillaries that at a given perfusion pressure whole blood tended to withdraw from the surrounding medium more fluid than did its own serum, as if the cells gave it a greater effective osmotic pressure. The explanation of this effect of the cells is not obvious. The membranes used by Schade and Claussen in their models were biologically inert, composed of collodion. Whether the increased tendency to edema in anemia be ascribed, as these experiments suggest, to the influence of cells in enhancing colloid osmotic pressure or to circulatory or nutritive disturbances increasing capillary pressure or permeability, it is in no way incompatible with the Starling theory. Edema and colloid osmotic pressure appear to be closely related, but the level of colloid osmotic pressure at which edema appears is higher than it is in malnutrition without anemia, just as it is higher in malnutrition than in the nephrotic syndrome⁵³ or in plasmapheresis.⁷⁶ Meulengracht, Iversen and Nakazawa⁴⁹ also found only moderate reductions of protein and colloid osmotic pressure in anemia patients with edema, and concluded that impaired circulation must play a part in promoting transudation.

Liver Diseases. The liver has been considered by many to be one of the important sites for the production of serum proteins, although direct evidence of such a function is lacking except as far as fibrinogen is concerned. This one fraction seems to be definitely a hepatic product. Evidence that albumin and globulin have a similar origin is unsatisfactory. It consists first of certain experiments in which Whipple and his associates³³ found that albumin and globulin were more slowly restored after plasmapheresis by animals with injured livers. However, the liver damage may well have acted merely by interfering with proper nutrition. Second, Starling⁷⁰ and others demonstrated that hepatic lymph contained more protein than did lymph from other organs and tissues. This Starling attributed not to the hepatic formation of proteins, but to greater permeability of liver capillaries. Finally, reductions of serum albumin noted by many observers in patients with severe liver damage^{1 6 57 71 77} have been referred by some to diminution of albumin formation in the liver, again without consideration of the effect of serious hepatic insufficiency upon general nutrition.

In Fig. 7 are presented a small number of observations from a group of patients suffering either from cirrhosis of the liver or from severe toxic liver destruction, chiefly the former. Examination of the albumin figures reveals the fact that low albumin is almost

invariably associated with obvious malnutrition. The relation of edema (which in these cases means ascites and edema of the lower extremities) to serum albumin and colloid osmotic pressure is not at all clear. Obviously the edema was chiefly due to circulatory obstruction. If an attempt were made to distinguish grades of edema and ascites, a better correlation would probably result. Moreover, it has appeared clinically as if patients with malnutrition and low albumin developed ascites at an earlier stage of the disease than did the well nourished with normal proteins. It seems at least highly probable that low serum albumin is, in many instances, a contributory cause of ascites.

Globulin lay above or in the upper range of the normal limits of variation in every case but one. This was a case of hemochromatosis with purpura and general anasarca examined in the last days of the

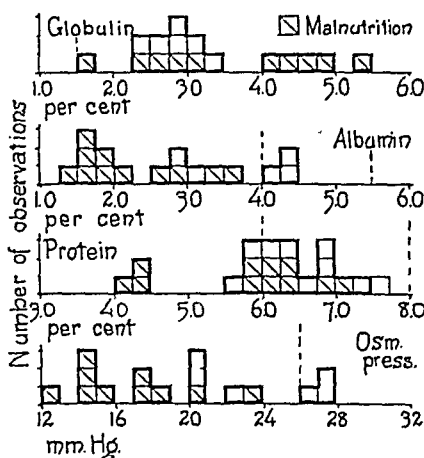


FIG. 7.—The serum proteins in patients with liver disease. Heavily outlined squares indicate the presence of edema. Limits of normal variation are marked by the broken vertical lines.

disease. Hyperglobulinemia has also been reported in cirrhosis by other observers,^{1 57 71 77} and after experimental liver injury by Sawada.⁵⁹ The highest values in this series were found in 3 patients, all of whom probably had biliary cirrhosis. The significance of the globulin increases is quite obscure. There appears to be little justification in the evidence thus far adduced, however, for the view that the liver plays an important part in the production of either albumin or globulin.

Miscellaneous. Figure 8 shows the results of examinations of a series of patients with miscellaneous conditions. They were selected from a larger number because they presented some abnormality of serum proteins or malnutrition, edema or dehydration. The largest single group suffered from gastro-intestinal diseases.

Globulin was increased in 9 instances. Three of these (3.74, 3.63 and 3.74 per cent) were subjects dehydrated by diarrhea or vomiting

and probably represent merely the results of hemoconcentration. This was clearly demonstrated in the second patient, whose globulin fell from 3.63 to 1.84 per cent after he had received adequate parenteral fluids. A value of 3.78 per cent was seen in a patient with a congenital cyst of the femur and a pathologic fracture. The high globulin may be a response to the injury or connected with the nature and situation of the cyst. Values of 3.36 and 3.33 occurred in a patient with arthritis deformans, and 3.02 was found in a case of Addison's disease. As the latter is so frequently caused by tuberculosis, the increase of globulin is probably connected with this infection, although no signs of the disease were discovered in

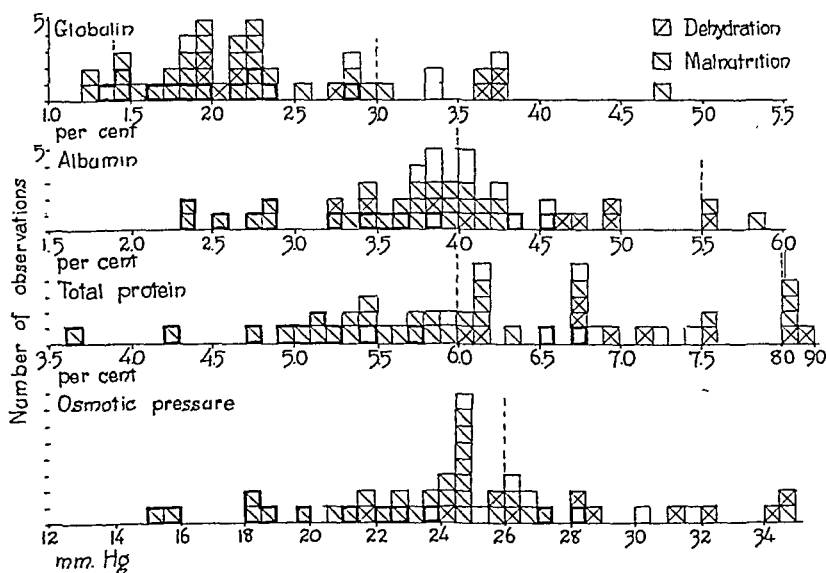


FIG. 8.—The serum proteins in patients with miscellaneous diseases. Heavily outlined squares indicate the presence of edema. Limits of normal variation are marked by the broken vertical lines. The total protein scale is reduced above 8 per cent.

other organs. One patient had a globulin of 3.66 per cent after a suprapubic cystostomy for cystitis which resulted from catheterization for paralytic urinary retention which developed during encephalitis. The last patient, with globulin 4.75 per cent, presumably had an infection, although its nature was not determined, because he had profuse albuminuria, petechial hemorrhages and a partial paralysis of the left side.

Again low albumin is usually associated with malnutrition. There are no exceptions to the rule with albumin less than 3.7 per cent. Of the 3 patients with albumin between 3.7 and 4 per cent who were not obviously malnourished, one was recovering from severe erysipelas which had undoubtedly caused wasting, another had arthritis deformans in an active stage, the third was suffering

from angioneurotic edema. Govaerts²³ has shown that in this condition the capillaries of the affected region become more permeable, allowing protein to escape with the edema fluid. During the development of edema of this character the serum proteins fell. Malnutrition was observed on 7 occasions with albumin above 4.5 per cent. In 5 instances there was obvious dehydration. Of the 2 remaining patients, 1 had a moderate, unexplained pyrexia, the other residual paralysis resulting from anterior poliomyelitis. Both subjects were thin, but not emaciated, and in neither was there any clear history of dietary deficiency.

Edema was invariably found when albumin was below 3 per cent, and 4 out of 22 times when it was between this level and the lower limit of normal, 4 per cent. In 3 of the 4 the edema was associated with generalized exfoliative dermatitis; in the 4th it was angioneurotic in character. In the 2 instances with albumin above 4 per cent the edema was also angioneurotic in origin. In all these cases circulatory disturbances were probably partly responsible for the transudation. In addition Govaerts²³ has demonstrated that the edema fluid in angioneurotic edema is relatively rich in protein, indicating that the permeability of the capillaries of the affected parts is increased.

Discussion. As far as the relation of edema to serum protein concentration and to estimated colloid osmotic pressure is concerned, the data as a whole lend ample support to the Starling theory if account is taken of all the forces which, according to the definition of this theory given above, determine the balance of fluid exchange between blood and tissues. This does not imply that there need be any exact correlation between edema production and the concentration of serum protein or any of its fractions; it does not even mean that there need be a critical level of protein, albumin or colloid osmotic pressure, below which edema inevitably occurs; because colloid osmotic pressure is only one of the forces concerned in the internal fluid exchange. In the absence of any obvious alteration of other forces, edema may be expected to appear in non-nephritic cases when albumin falls to about 3 per cent. Exceptions to this rule in diabetes, carcinoma, infections and a variety of miscellaneous diseases are found under certain particular circumstances: (1) if globulin is increased sufficiently to compensate for the osmotic deficiency created by the serum albumin depletion; (2) if the patient is dehydrated by vomiting, diarrhea or abstention from fluids. In the latter case materials for the production of edema are withdrawn from the body or prevented from gaining access to the body. Perhaps, in the definition of the Starling theory the fluid and salt available for the formation of edema must be included among the forces which determine transudation. If transudation and reabsorption of fluid from and to the capillaries are, under any given conditions, in a state of equilibrium, withdrawal of fluid from the

blood through kidneys, gut or skin will necessarily lead to readjustment of equilibrium by the reabsorption of a certain amount of fluid from the interstitial fluids into the capillaries. For the same reason, administration of large quantities of fluid and salt may cause edema to appear at colloid osmotic pressures higher than those at which it is usually encountered. Edema was found when albumin exceeded 4 per cent chiefly in the presence of heart failure or other circulatory disturbances which are known to increase capillary blood pressure. In a few instances there is reason to attribute edema at high albumin levels to increased capillary permeability. In the intermediate zone between 3 and 4 per cent edema occurred with some frequency. Evidence of some one of the contributory causes of edema already mentioned could be found in the majority of the subjects in this group, especially as the proteins approached the normal limits. Theoretically edema should be more closely correlated with colloid osmotic pressure than with albumin. However, the difference is only appreciable in the tumor group of this series, because only in myelomatosis was albumin below 3 per cent associated with globulin sufficiently high to raise the colloid osmotic pressure into the normal range. It has been demonstrated in the case of myelomatosis here reported, as in the case reported by Perlzweig, Del Rue and Geschickter⁵² and a nephrosis case of Salvesen,⁵³ that, in accordance with the Starling theory and estimations of the relative osmotic pressures of the two protein fractions, when albumin falls to the level at which edema may be expected, edema will not occur if globulin is sufficiently increased to make up the osmotic deficit. Anemia increases the tendency to edema and raises the albumin and the osmotic pressure at which it may be expected to 4 per cent and 26 mm. Hg respectively.

With few exceptions reductions of serum albumin can be directly related to malnutrition if this term is defined, not with reference to the state of preservation of adipose tissue, but as denoting a condition in which body proteins have been recently depleted or are being actively depleted. It has been suggested that malnutrition in this sense is compatible with the presence of obesity. Moreover, it appears that during the restoration of body protein serum albumin may rise to normal limits before a normal nutritive state has been attained. Exceptions to the general relation of albumin to the state of preservation of body protein are no commoner than one might expect when the difficulties of determining the exact nutritive state are taken into consideration. This is true not only in patients with diabetes, tumors and miscellaneous diseases, but even in those with marked impairment of hepatic function. In few cases is there any reason to hypothecate leakage of protein from the blood stream or any other mechanism to explain the albumin deficits. It follows that the investigation has thrown no light on the site of production of this protein fraction.

If the albumin and colloid osmotic pressure deficits are referable only to malnutrition, the critical level for edema production, 3 per cent, applies only to malnutrition edema. It is distinctly above the similar level which Peters, Bruckman, Eisenman, Hald and Wakeman⁵⁴ found in the nephrotic syndrome. The difference may be only partly connected with the distinctive pathologic conditions involved, in part connected with the fact that in the nephritic cases therapeutic measures were more frequently directed specifically to the elimination of edema. However, it is not unlikely that edema does occur at higher osmotic pressures in malnutrition than in nephrosis, just as it occurs at higher levels in malnutrition than after plasmapheresis.

Globulin is high in patients with certain types of neoplasms, especially myelomatosis, and possibly certain other tumors affecting the bone marrow. In the great majority of patients, however, with benign or malignant tumors it remains quite normal. Slight increases may accompany a great variety of infections; but increases of considerable magnitude were observed only in suppurative infections, and ulcerative tuberculosis and syphilis. In cirrhosis of the liver, also, globulin may rise far above the normal level. It is difficult to draw any exact conclusions concerning the origin of globulin or the stimuli to its production from such unrelated data. The difficulty may lie partly in the heterogeneous nature of the proteins of which the globulin fraction is composed. Within moderate limits hyperglobulinemia may be produced by hemoconcentration.

Reductions of total protein are usually referable to albumin deficits, increases to excess of globulin. The correlation between total protein concentrations and any one of the disorders of function which may affect the two fractions is far from satisfactory, as is evident from all the figures. It is almost unnecessary to say that the study emphasizes the meaninglessness of the "albumin: globulin ratio."

Summary and Conclusions. From an analysis of 109 total protein determinations from 52 individuals and of 50 protein fractions from 34 individuals, the following limits of normal variation have been defined: for total protein, 6 to 8 per cent; albumin, 4 to 5.5 per cent; globulin 1.4 to 3 per cent. Globulin in excess of 2.5 per cent was found only in the winter months and may represent effects of respiratory infections which are so prevalent in this climate at that season.

Total proteins have been determined 542 times in 374 patients suffering from various diseases which do not affect directly the cardiovascular or renal systems, and in 215 of these subjects 332 determinations of protein fraction have been made. The data have been analyzed from various points of view and the following conclusions have been drawn.

The relation between edema and the estimated protein osmotic pressure is in keeping with the theory of Starling.

Reductions of albumin can be connected almost invariably with malnutrition.

Increases of globulin are found with infections, especially suppurative processes and ulcerative tuberculosis or syphilis; in connection with certain tumors, particularly myelomata; and in cirrhosis of the liver.

The study has thrown no light on the sites of production of the two protein fractions.

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CLINICAL NOTES ON RHEUMATIC HEART DISEASE WITH SPECIAL REFERENCE TO THE CAUSE OF DEATH.*

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ANY extensive experience in the care of those suffering with rheumatic heart disease discloses a great variability in the course such patients run, the duration of life and in the complications that they manifest, though the exact reasons for this are far from clear.

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One patient with valvular heart disease carries on in comparatively good health for a great many years and another who starts with apparently the same lesion succumbs in a short while. Death is often ascribed to heart failure when a closer analysis of events reveals that a more specific complication which cannot be regarded as ordinary circulatory failure was the direct cause of the fatality. In other words, not all patients with rheumatic valvular disease die in the same way nor does congestive heart failure account for many of the deaths with this disease. With this in mind a careful study was made of all the cases of rheumatic heart disease in which postmortem examination was performed at this hospital from 1913 to 1932, who died as a result of their cardiac lesions. Cases with valvular disease who died after some surgical operation, of cancer, or of any other unrelated condition were therefore excluded. Although our main purpose was to investigate the factors that were particularly responsible for the fatality, certain other clinical considerations of interest were uncovered.

The 148 cases included in this review (Table 1) were divided into five different groups. The first contained all the cases that died of congestive heart failure in which none of the other factors discussed below were material as a cause of death (49 cases). The second group included 34 cases in which death resulted primarily from an acute infection, which may be considered essentially as an acute rheumatic carditis. The third group of 17 cases were those in which emboli and thrombi were directly responsible for the terminal illness. Subacute bacterial endocarditis (43 cases) made up the fourth group. There remained 5 cases of a heterogenous type that could not be included in any of the above classifications, which comprised a miscellaneous fifth group. It contained 2 cases of death from quinidin therapy and other sudden deaths in cases with aortic disease, with or without pulmonary edema. It is apparent from this method of classification that in the second, third, and fourth groups death was precipitated by what one might call an accident of heart disease occurring frequently many years before heart failure of the congestive type would otherwise have been expected. Had these accidents not taken place, the patients might have remained in a state of moderate or excellent compensation for a considerable period of time. It is obvious therefore that most patients suffering from rheumatic heart disease do not die from congestive heart failure. This study in addition to ascertaining the frequency of the various modes of death, also investigated the factors which might have determined the course which an individual patient pursued.

Congestive Heart Failure. Of these 49 cases the sexes were about equally involved (Tables 1 and 2). The ages were proportionately distributed among the various decades.* The largest number of fatalities occurred in the fifth decade. Twenty-four had a positive

* As children under 12 years of age are not admitted to this hospital the first decade is not represented here.

TABLE 1.—CAUSE OF DEATH.

	Number.			Average age at death.	Duration of symptoms (in years).	Past history.				Valvular lesions.					Rhythm.		Heart weight.	Myocardium.		
	Male.	Female.	Total.			Negative.	Rheumatic fever.	Chorea.	Rheum. fever and chorea.	Aortic.	Mitral.	Aortic, mitral.	Mitral, tricuspid.	Aortic, mitral, tricuspid.	Regular.	Atrial fibrillation.		Normal.	Moderate fibros. s.	Extensive damage.
Congestive failure	23	26	49	40.5	4.2	17	24	4	4	8	9	13	7	12	21	28	617	26	19	4
Acute rheumatic carditis	10	24	34	30.6	1.9	5	21	1	7	1	2	17	3	11	22	12	549	10	3	21
Emboli and thrombi	12	5	17	40.0	3.8	5	11	0	1	2	9	1	1	4	1	16	551	7	9	1
Subacute bacterial endocarditis	26	17	43	38.2	0.5*	24	16	1	2	8	17	15	2†	1	41	2	449	Not studied		
Miscellaneous	5	5	32.8	9.2	..	3	..	2	2	2	1	2	3	654	2	2	1
Total	71	77	148	37.2	2.7	51	75	6	16	19	37	48	15	29	87	61	546	45	33	29

* Approximate.

† Aortic and tricuspid.

history of rheumatic fever, 4 of chorea, 4 had both, and 17 had a negative history. Eight cases had involvement of the aortic valve, for the most part producing varying degrees of stenosis. Nine had mitral lesions, 13 had aortic and mitral involvement, 7 had mitral and tricuspid, and 12 had aortic, mitral and tricuspid disease. The lesions practically always produced stenosis of these valves. The state of the myocardium as indicated by pathologic examination was designated as being normal, moderately fibrosed, or showing extensive damage. There were 26 that were regarded as normal, 19 with moderate fibrosis and 4 with extensive changes in the myocardium. For the most part throughout this study the ventricular musculature was not greatly involved except in the acute cases.

Concerning the occurrence of embolism and thrombosis, in 16 none were found, 26 showed pulmonary infarcts, 5 had cerebral emboli, 8 had renal infarcts, and there were 3 miscellaneous cases (Table 6). The great frequency of pulmonary infarction is noteworthy. It was usually accompanied by a mural thrombus in the right auricle (16 instances, right auricle, in 8 of which they were also found in the left auricle). There were 4 additional cases with thrombi confined to the left auricle. In the other 29 cases no mural thrombi were present. It is necessary and reasonable to assume that pulmonary infarction frequently resulted from local thromboses of the pulmonary vessels consequent to a prolonged passive congestion of the lungs. In no cases were the emboli or thromboses regarded as the deciding factor in the cause of death. It is interesting that although there were 26 cases of pulmonary infarction, in only 18 was there any evidence of hemoptysis. The absence of bloody sputum, therefore, is no indication that infarction of the lung did not occur.

TABLE 2.—VALVULAR LESIONS IN "CONGESTIVE FAILURE."

	Number.	Regular.	Auricular fibrillation.	Heart weight.	Duration of dyspnea.	Average age.
Aortic	8	6	2	669	1.5	50 1
Mitral	9	2	7	475	3.7	48.1
Aortic and mitral	13	8	5	726	4.7	39.0
Mitral and tricuspid	7	2	5	551	6.2	27 4
Aortic, mitral and tricuspid	12	3	9	611	4.5	37.6
Total	49	21	28	617	4.2	40.5

The rhythm of the heart in this group was frequently grossly irregular. Auricular fibrillation was present in 28 (one of these had auricular flutter for a while) and 21 showed a regular rhythm. This reflects the great importance of auricular fibrillation as an underlying finding in rheumatic patients who succumb to congestive heart failure. This was particularly true of the cases with mitral stenosis alone, although there were two who died with a regular rhythm (Table 2).

When the aortic valve was involved either alone or in combination with one of the other valves, death with a regular rhythm was more common. The contrast between the rhythm in the cases with pure aortic and pure mitral lesions was quite striking: whereas there were only 2 out of 8 cases with auricular fibrillation in the former, there were 7 out of 9 in the latter. Patients with aortic disease much more commonly die of congestive heart failure with a regular rhythm than do those with a mitral disease. When the aortic or tricuspid is involved in addition to the mitral valve, the incidence of regular rhythm lies somewhere between these two. Of 32 such cases, there were 13 with a regular rhythm and 19 with auricular fibrillation. Analyzed from a different point of view, it was found that 21 cases died with a regular rhythm and all but 4 had aortic stenosis with or without other valvular disease. Furthermore, of the 28 who had auricular fibrillation all but 2 had mitral stenosis. Finally, 13 of the 15 cases of mitral stenosis who died with a regular rhythm had other valvular lesions. The inference to be drawn from the above considerations is that patients of this type who have auricular fibrillation have mitral stenosis almost invariably and that if the rhythm is regular they are very apt to have aortic stenosis alone or in combination with mitral stenosis.

The duration of life after the first evidence of troublesome dyspnea was investigated in the different types of valvular disease. In the 8 cases in which the aortic valve alone was stenosed, death occurred 1.5 years and in the 9 cases of mitral stenosis death occurred 3.7 years after the onset of dyspnea. Where more than one valve was involved the duration of life after dyspnea began seemed to be somewhat greater. This was particularly true in the 7 cases of mitral and tricuspid stenosis, which had a duration of 6.2 years. This latter fact has a certain clinical significance, for it indicated that the finding of involvement of more than one valve does not mean a poorer prognosis after symptoms have developed, but contrariwise it may be expected that the length of life thereafter may even be a little greater than if only one valve were affected. On the other hand, although the average duration of life after dyspnea develops is greater, the age at death is younger than in those cases with single lesions. The average age at death of those with aortic stenosis alone was 50.1 years and with pure mitral stenosis 48.1 years. The cases of combined aortic and mitral disease and aortic, mitral and tricuspid died at the average ages of 39 and 37.6 years respectively, while those with mitral and tricuspid disease lived to an average age of only 27.4 years.

Acute Rheumatic Carditis. The second common cause of fatality in rheumatic heart disease is acute rheumatic infection. The clinical course these patients ran was fairly characteristic. There was usually persistent moderate fever, a rapid heart rate and anemia. Over half developed congestive failure during the acute attack and

the usual therapeutic measures were of no avail. The pathology was that of an acute pancarditis with small pearly vegetations along the valve leaflets, Aschoff bodies in the myocardium, and an acute fibrinous pericarditis in many.

There were 34 such cases in this series (Tables 1 and 3). In each instance it seemed fairly clear that an acute rheumatic carditis was directly responsible for death and that, had this infection not occurred, these patients would have been expected to live for a number of years. For the most part they were patients who, directly before the terminal infection, showed no evidence of congestive heart failure. There were 24 females and 10 males. Almost half were under 20 years of age and about two-thirds were under 30. This group therefore comprises a larger number of younger cases than any other in the entire study and it follows that rheumatic infection as a direct cause of death is most to be feared in younger individuals.

TABLE 3.—VALVULAR LESIONS IN "ACUTE RHEUMATIC CARDITIS."

	Number.	Regular.	Auricular fibrillation.	Heart weight.	Duration of dyspnea.	Average age.
Aortic	1	1	..	720	0.2	68.0
Mitral	2	1	1	395	1.1	40.0
Aortic and mitral	17	12	5	600	1.7	26.4
Mitral and tricuspid	3	2	1	586	0.1	30.0
Aortic, mitral and tricuspid	11	6	5	435	3.1	31.9
Total	34	22	12	549	1.9	30.6

A previous history of rheumatic fever was obtained in 28 instances, 7 of whom also had chorea. There was 1 who had only a history of chorea and 5 who had no history either of rheumatic fever or chorea. It is evident that patients with a past history of chorea alone very rarely succumb to an acute rheumatic carditis.

Involvement by the acute process of a single valve was rare, occurring once on the aortic and twice on the mitral valve. There were 3 with combined mitral and tricuspid lesions, 17 aortic and mitral, and 11 aortic, mitral and tricuspid. It is no simple matter at times, when examining these hearts postmortem, to distinguish changes in the valves resulting from the acute as contrasted with the chronic process. However, 30 of the 34 patients seemed to show evidence of previous valvular damage, but the site of this prior lesion was not always involved in the terminal acute process. In 2 the chronic process was limited to the aortic valve and in 7 to the mitral. Fifteen showed chronic disease of the aortic and mitral, 1 of the mitral and tricuspid, and 5 of the aortic, mitral, and tricuspid valves. Here, as in the previous group of patients who died of congestive heart failure, in general the younger patients showed a larger number of valves involved.

This group as a whole showed far more extensive damage of the myocardium than any of the other groups. In 13 the heart muscle was normal or only moderately fibrosed, while 21 exhibited marked myocardial changes. This was the only group in which there was any pathologic evidence to indicate that the state of the myocardium was a pertinent factor in the causation of congestive heart failure.

Emboli and thrombi were of minor significance (Table 6). Eleven of these patients had small pulmonary infarcts, 5 had renal infarcts and there were 2 with miscellaneous thromboses. Only 7 of the 18 patients with thrombosed vessels had mural thrombi in the auricles. The inference from this is that small infarctions can develop in the peripheral organs either as a result of local thromboses or from miliary emboli coming from a small rheumatic vegetation on the valves. One need not postulate the presence of thrombi in the auricles to explain these changes.

The rhythm in this group was predominantly regular. However, there were 12 with auricular fibrillation and 22 who maintained a regular rhythm. In every instance of fibrillation, a mitral lesion was present, while 19 of the 22 with a regular rhythm had aortic valve damage.

The length of life after the onset of dyspnea and other evidence of circulatory insufficiency was on the whole rather short in this group of cases as contrasted with those discussed above who died of congestive heart failure. The average for the entire group was 1.9 years whereas for the patients who died of congestive failure it was 4.2 years. This does not refer to the duration of symptoms after the acute process had developed, as this was much shorter, often only weeks, but difficult to measure accurately.

Emboli and Thrombi. The third group of patients in this study comprised those in whom an embolus or thrombosis of a vessel was the determining factor in the causation of death. There were 17 such instances. From a clinical review of this group it was apparent that these cardiac accidents were directly responsible for the fatality and had they not occurred, congestive heart failure would not have developed and they might have been expected to live for a considerable length of time.

TABLE 4.—VALVULAR LESIONS IN "EMBOLI AND THROMBOSES."

	Number.	Regular.	Auricular fibrillation.	Heart weight.	Duration of dyspnea.	Average age.
Aortic	2	..	2	645	1.5	54.5
Mitral	9	..	9	490	2.5	38.3
Aortic and mitral	1	..	1	440	10.0	46.0
Mitral and tricuspid	1	..	1	520	6.0	41.0
Aortic, mitral and tricuspid	4	1	3	680	5.8	34.5
Total	17	1	16	551	3.8	40.0

TABLE 5.—SUMMARY OF VALVULAR LESIONS.

	Cause of death.					Rhythm.		Heart weight.	Duration of dyspnea.	Average age at death.	Past history.	
	Congestive failure.	Acute rheumatic carditis.	Emboli and thrombi.	Miscellaneous.	Total.	Regular.	Auricular fibrillation.				Pos.	Neg.
Aortic	8	1	2	..	11	7	4	669	1.4	52 5	4	7
Mitral	9	2	9	..	20	3	17	474	2.9	42 8	11	9
Aortic and mitral	13	17	1	2	33	22	11	663	3.5	31.6	29	4
Mitral and tricuspid	7	3	1	2	13	4	9	555	6.1	30.5	10	3
Aortic, mitral and tricuspid	12	11	4	1	28	10	18	557	4.0	35.1	24	4
Total	49	34	17	5	105	46	59	586	3.6	36 8	78	27

There were 12 males and 5 females (Table 1). In 12 cases a past history of rheumatic fever was present, 1 of which had chorea. There were none with a past history of chorea alone, and 5 had no previous history of either. Fifteen of the cases had mitral stenosis, of which 1 had aortic stenosis in addition, 1 had tricuspid stenosis, and 4 had aortic and tricuspid stenosis (Table 4). In only 2 was there aortic stenosis unassociated with other valvular disease. This type of complication therefore predominately occurs in those patients who have mitral disease.

Embolism and thrombosis were often multiple and it was then difficult to estimate which one was the more important factor in causing the fatality (Table 6). Postmortem examination of the brain was not made in all instances and no doubt there were more

TABLE 6.—EMBOLI AND THROMBI.

	Location.				Hemorrhage.		Mural thrombi.		
	Pulmonary.	Cerebral.	Renal.	Other.	Hemoptysis.	Hematuria.	Right auricle.	Left auricle.	Both.
Congestive failure	26	5	8	3	18	3	8	4	8
Acute rheumatic carditis	11	..	5	2	9	3	2	1	4
Emboli and thrombi	14	7	4	5	6	1	2	4	2
Miscellaneous	1	2
Total	52	12	17	10	33	7	14	9	14

occurrences of cerebral embolism than were detected by our study. The pulmonary emboli and infarctions were for the most part large and extensive. There were 14 such cases. There were 7 cerebral lesions, 4 renal infarcts, and 5 in the miscellaneous group. Among the latter were mesenteric thromboses, and occlusion of the popliteal and coronary arteries. When emboli occurred in these cases they

resulted from the dislodgment of mural thrombi which had previously formed in the auricles. They did not come from the valves of the heart as occurs in bacterial endocarditis or from the ventricular walls as in coronary thrombosis. Two cases showed mural thromboses of the right auricle, 4 of the left auricle, and 2 of both. In the 9 instances that were reported as having no mural thrombi a more careful examination of the auricular appendages might have revealed further instances of mural thrombosis.

Hemoptysis occurred in only 6 instances. This is explained by the fact that in some cases death occurred rather quickly after a pulmonary embolus and in others definite pulmonary infarction was present without any clinical evidence of bloody expectoration. It is impossible to correlate the finding of renal infarct with the presence of hematuria. This was because examination of the urine was carried out at irregular intervals and may not have been done at the time of renal infarction.

The rhythm of the heart in the 17 cases of this group was grossly irregular in every instance but one. This is a striking confirmation of the prevailing impression that auricular fibrillation is an important predisposing factor in the formation of mural thrombi and peripheral emboli. In none of the groups contained in this study was the incidence of auricular fibrillation so great.

The relation between the state of compensation of the circulation and the development of emboli and thromboses is of some interest. In 5 of the 17 cases, these circulatory accidents occurred without any previous evidence of congestive failure. In 9 they occurred during the first break in compensation. One took place during the second and 2 during the third break in compensation. In practically all of these cases where cardiac failure had taken place, compensation had been very well restored before embolism or thrombosis had occurred. One gains the impression that this type of accident is apt to occur while the state of compensation is fairly satisfactory.

The average age at death of these patients was 40 years and the duration of life after the first evidence of dyspnea was 3.8 years. This latter figure was slightly but distinctly less than the corresponding figure for the group who died of congestive heart failure.

Subacute Bacterial Endocarditis. The number of patients with rheumatic heart disease who died of subacute bacterial endocarditis was surprisingly great. Of the 148 cases in the entire study 43 (29 per cent) died of this disease. This is almost as many as the number that died of congestive heart failure. In 2 of these cases the review of the clinical and pathologic data was open to double interpretation. In some ways they resembled an acute bacterial infection of previously damaged valves and in some ways conformed to the picture of subacute bacterial endocarditis. There were 26 males and 17 females. There was a past history of rheumatic

fever in 18 instances 2 of which also had chorea, and only 1 had a past history of chorea alone (Table 1).

The vegetations were confined to the aortic valve in 8 cases, to the mitral in 17, and involved both of these valves in 15. Two showed vegetations on the aortic and tricuspid valves and 1 on the aortic, mitral and tricuspid valves.

The average age at death in this group was 38.2 years. Auricular fibrillation was present before the development of subacute bacterial endocarditis in only 1 case, and 1 additional patient had transient auricular fibrillation during the course of the infection. There was not a single instance of gross congestive failure preceding the onset of this disease, although many cases developed failure of the congestive type before they died.

Other features such as the type of chronic valvular disease with which this infection is associated and the site of embolism were not analyzed because such a study has recently been made.¹

In general it may be said that this group contained patients with valvular disease who had a regular rhythm, who were in comparatively good health, never having shown evidence of congestive heart failure, and who succumbed at a relatively young age.

Miscellaneous Group. There remained 5 cases that could not be classified in any of the above four groups. Two of these patients had mitral stenosis and auricular fibrillation and died suddenly during the administration of quinidin. Death was not due to emboli. There were 2 other cases that died from acute pulmonary edema. One had well-marked mitral and tricuspid stenosis and the other a marked aortic stenosis with only slight mitral involvement. The last case was a young girl 19 years of age who had aortic and mitral disease and attacks of angina pectoris. She died suddenly and unexpectedly in what was probably an attack of angina. These cases illustrate the more unusual causes of death in valvular heart disease and no doubt with a more extensive experience other rare mechanisms will be found.

Age at Death. The average age at death of the 11 cases with aortic valve disease alone was 52.5 years (Table 5). The oldest was 71 and the youngest 30. There was only 1 under 43 years of age. This group of cases had the highest average age. The average age at death of 20 cases of mitral stenosis unassociated with other valvular disease was 42.8 years or 10 years less than the aortic group. The youngest was 12 and the oldest 68 years of age (children under 12 were not included in this study). When aortic and mitral disease were both present the average age at death of 33 cases was 31.6 years. The youngest was 12 and the oldest 59. Of the 13 cases with mitral and tricuspid stenosis the average age at death was 30.5 years with similar age limits. The last group that showed aortic, mitral, and tricuspid stenosis (28 cases) had an average age at death of 35.1 years. One can infer from these figures that

stenosis of the aortic valve unassociated with other valvular disease matures at an older age than does any other individual or combination of valve lesions. Furthermore, when the aortic or tricuspid or both valves are involved in addition to the mitral, the average age at death is approximately the same.

The cases of subacute bacterial endocarditis formed such a distinct group that it seemed proper to analyze them separately. The average age of this group was 38.2 years and the range extended from the ages of 17 to 66.

Sex. A study of the sex distribution in the various groups of cases was of some interest. Among the 49 cases who died of congestive heart failure, there were 23 males and 26 females. Of the 34 cases that died of acute rheumatic carditis, there were 10 males and 24 females. In the group with emboli and thrombi, there were 12 males and 5 females, and finally in the 43 cases of subacute bacterial endocarditis, there were 26 males and 17 females. There was a distinct predominance therefore of the females in those who died of an acute infection and of the males in those who died of emboli and thrombi or subacute bacterial endocarditis.

Past History of Rheumatic Infections. It is current knowledge that a past history of rheumatic infection such as rheumatic fever or chorea can be obtained in only a portion of the cases that suffer from that type of valvular disease which is regarded as rheumatic in nature. Frequently the adult has forgotten or never was told that he had a rheumatic infection in childhood. More often he had an infection that was atypical in course which, although rheumatic in nature, was regarded as some other type of illness. It is therefore not to be expected that a past history can be obtained in 100 per cent of the cases of definite rheumatic heart disease. The greater the number of recurrent bouts of rheumatism or chorea and the younger the patient when questioned, the higher will be the incidence of a positive past history. The figures that follow well indicate these divergences. Of the 11 cases of aortic stenosis, there were only 4 that had a positive past history. In 11 out of 20 with mitral stenosis the past history was positive. Twenty-nine out of 33 with aortic and mitral stenosis, 10 out of 13 with mitral and tricuspid stenosis, and 24 out of 28 with stenosis of the aortic, mitral and tricuspid valves had a positive past history (Table 5). Finally, among the 43 cases of subacute bacterial endocarditis, 19 had a previous history of rheumatic fever or chorea (Table 1).

We believe that practically all of the cases in this study, including those with a negative past history, had had a previous rheumatic infection. The higher incidence of a positive history among those in whom more than one valve was involved may have been due to the fact that the initial infection was more violent, more typical in its characteristics or that more than one attack occurred. The natural result would be that an affirmative answer concerning a

previous history would be more apt to be obtained. Although it is generally accepted that mitral stenosis is almost invariably due to a previous rheumatic infection, a similar view is not held in relation to aortic stenosis which is frequently regarded as due to arteriosclerosis. We believe, however, that acquired stenosis of any valve is practically the sole result of an earlier rheumatic infection. We feel that the frequent finding of calcification of the aortic valve in no way militates against this view. The so-called "arteriosclerotic aortic stenosis" we feel is not unlike the similar type of mitral stenosis in its etiology. Calcification occurs not infrequently in rheumatic disease of both valves, although it is more apt to be present in the aortic valve in older people. It is for this reason that it has been regarded as arteriosclerotic. Very commonly in such older cases, however, the wall of the aorta which is the customary site for sclerotic changes is particularly normal in appearance. It is more than likely that if all the details of the early illnesses had been known of our patients with aortic stenosis, even a larger proportion would have been identified as being rheumatic. It is sufficient that approximately 50 per cent of the cases of aortic stenosis with calcification had a past history of rheumatism, as was found by Christian,² to consider that in practically all was rheumatism the etiologic factor. This apparently anomalous inference is supported by the frequent finding in various studies that only 50 per cent of cases with *mitral* stenosis have a positive history. One should therefore expect even a lower percentage in cases of aortic stenosis as they are seen on the average 10 years later in life.

There is an interesting relationship between the type of initial infection and the eventual character of the cardiac damage. Strong³ found that in a given number of cardiac patients who had a past history of chorea alone about nine-tenths would show involvement of the mitral valve and only one-tenth of the aortic valve. Acute pericarditis was rare in this group. On the other hand if a similar number of valvular cases were studied who had a past history of rheumatic fever alone, about 60 per cent would show mitral involvement, 30 per cent aortic involvement and about 10 per cent acute pericarditis. This review, which includes only cases that were examined postmortem does not permit an investigation of this relationship as there were only 6 instances in which chorea had occurred in the past unassociated with rheumatic fever. It is of some interest to note that of the 43 cases of subacute bacterial endocarditis only 1 had a past history of chorea alone. Despite the comparative infrequency of chorea it seems that it is especially rare as a predisposing illness to bacterial endocarditis.

Valvular Lesions. Excluding the 43 cases that died of subacute bacterial endocarditis there were 105 which showed valvular disease of one sort or another. In referring to disease of the valves in this latter group, it is meant that the valve is stenosed to a greater

or lesser degree. In the majority of instances, no matter which valve is considered this stenosis was well marked. There were 11 cases of aortic valvular disease, 20 of mitral, 33 of aortic and mitral, 13 of mitral and tricuspid, and 28 of aortic, mitral, and tricuspid (Table 5). Although involvement of the mitral valve predominated, organic lesions of the aortic and tricuspid were quite common, which is in agreement with the findings of Boas.⁴ The recent statement by Lewis⁵ that stenosis of the aortic valve is infrequent cannot be substantiated by this pathologic study.

The chronic lesions in the 43 cases of subacute bacterial endocarditis were of a somewhat different nature. Although evidence of previous damage was present, the degree of stenosis was much less and marked stenosis was very rare. The final bacterial involvement, however, was always engrafted on a previously injured valve. The distribution of the vegetations on the three valves under consideration was as follows: 8 on the aortic, 17 on the mitral, 15 on the aortic and mitral, 2 on the aortic and tricuspid, and 1 on all three valves.

Cardiac Rhythm. The only irregularity investigated in this study was the presence or absence of auricular fibrillation and its influence on the type of death. There were very striking differences in this regard in the various groups (Tables 1 and 5). Among the 49 patients who died with congestive heart failure, 28 (57.1 per cent) had auricular fibrillation. Of the 34 cases that died of acute rheumatic carditis, 12 (35.3 per cent) had auricular fibrillation. All but 1 of the 17 in the embolic and thrombosis group had this irregularity. In contrast to the above groups in which this arrhythmia is so common, persistent auricular fibrillation occurred only once in the 43 cases of subacute bacterial endocarditis. There was 1 additional case in which this irregularity was a terminal event occurring just before death.

Recently Davis and Weiss⁶ concluded that the apparent rarity of auricular fibrillation in subacute bacterial endocarditis was accidental. They felt that subacute bacterial endocarditis would naturally occur predominately in regular hearts merely because there were more rheumatic cases with a regular rhythm than with auricular fibrillation. We feel that the great disparity and antagonism between these two conditions cannot be explained in this manner. There is a large number of patients with persistent auricular fibrillation and valvular disease who live on the average for several years. If the bacterial invasion of damaged valves were a mere accident, it is surprising that there are not more instances of subacute bacterial endocarditis in patients with auricular fibrillation. This same principle applies to the relation of congestive heart failure and subacute bacterial endocarditis. Davis and Weiss⁶ explain that the rarity of the former preceding the latter is a coincidence. If this were so it is still very difficult to explain why a

large number of valvular patients who suffer from congestive failure over a period of years never develop this bacterial type of infection of their valves.

Heart Weights. There were interesting variations in the weight of the heart in the different groups (Table 1). Considered from the point of view of the type of death, those who died of congestive heart failure had the largest hearts. The average weight of 49 such cases was 617 gm. The average weight of those dying of acute rheumatic carditis or of emboli and thromboses was about the same, 549 gm. for the former, 551 gm. for the latter. The group with subacute bacterial endocarditis had the smallest hearts, the average of 43 such cases being 449 gm. These figures make a fairly logical sequence when it is appreciated that subacute bacterial endocarditis may be regarded as an accident that develops in younger well-compensated heart patients and that emboli and thrombi also are accidents that occur before the complete picture of cardiac failure would be expected. Those dying of congestive heart failure may be considered as having escaped these fatal accidents and therefore as having lived longer with their cardiac disease to develop larger hearts.

There was in addition some relationship between the weight of the heart and the valvular lesion (Table 5). Although the number of cases in the various groups was not great, the figures seem to have a definite significance. The average weight of the heart of 11 cases with aortic disease was 669 gm. In contrast with this the average of 20 cases with mitral disease was only 474 gm. When the aortic and mitral were both involved the weight of the heart was about the same as in pure aortic cases; the average of 33 with this combination was 663 gm. When the mitral and tricuspid or mitral, tricuspid and aortic were all affected the averages were the same. The figures for the 13 cases of the former was 555 gm. and for the 28 cases of the latter was 557 gm. The aortic cases with or without mitral stenosis have the largest hearts, the pure mitral cases have the smallest, and those with combined tricuspid disease are midway between.

Although there was considerable overlapping in the weight of the heart in comparing individual cases of one group with another, the largest heart in which the mitral valve alone was involved was essentially no greater than the smallest with an aortic lesion whether the mitral valve was also affected or not. The figure for the former was 575 gm. and for the latter approximately 550 gm. The above weights which were obtained on postmortem examination must not be confused with the size of the heart as determined by bedside or roentgenologic examination. The element of dilatation of the chambers of the heart which plays such an important rôle in determining the outline of the silhouette was not investigated in this study. Clinically, the hearts that show the largest Roentgen ray shadows are more apt to be those with well-marked mitral stenosis

and huge dilatation of the auricles. The heaviest hearts with aortic stenosis do not as a rule produce such large Roentgen ray shadows.

Adhesive Pericarditis. A study was made of the effect of adhesive pericarditis on some of the other factors that have been discussed above. No attempt was made to differentiate minor from major adhesions. In general, however, it may be said that in most of the cases the adhesive pericarditis was well marked and frequently the entire pericardial cavity was obliterated. The average weight of 62 cases with a normal pericardium was 534 gm. The average weight of 43 cases with adhesive pericarditis was 654 gm., an increase of 120 gm. The cases of subacute bacterial endocarditis were not included in this calculation. The effect of pericardial disease on the weight of the heart in various types of valvular disease is shown in Table 7. It is evident that adhesive pericarditis adds appreciably to the weight of the heart.

TABLE 7.—INFLUENCE OF ADHESIVE PERICARDITIS ON WEIGHT OF HEART.

Valvular lesions.	With pericarditis.		Without pericarditis.	
	Number.	Weight.	Number.	Weight.
Aortic	3	663	8	671
Mitral	9	449	11	472
Aortic and mitral	16	761	17	564
Mitral and tricuspid	7	607	6	495
Aortic, mitral and tricuspid	8	706	20	498
Total	43	654	62	534

TABLE 8.—RELATION OF PERICARDITIS TO AGE AT DEATH.

Type.	Under 40.		Over 40.	
	Total.	With pericarditis.	Total.	Without pericarditis.
Congestive failure	21	8	28	7
Acute rheumatic carditis	25	16	9	2
Emboli and thrombi	7	4	10	3
Miscellaneous	4	3	1	0
Subacute bacterial endocarditis	23	4	20	2
Total	80	35 (43.7%)	68	14 (20.6%)

It is also of interest that with increasing age there was a tendency for adhesive pericarditis to become less frequent (Table 8). Among 80 cases under 40 years of age there were 35 with adhesive pericarditis (43.7 per cent). In the 68 cases over 40 years of age there were only 14 with pericardial adhesions (20.6 per cent). There was a striking difference in the frequency of pericardial adhesions in the 49 that died of congestive heart failure as contrasted with the group of 43 that died of subacute bacterial endocarditis. Fifteen of the former and only 6 of the latter showed pericardial disease. It is not surprising that the largest incidence occurred in those that died of acute rheumatic infection. In this group of 34 there were 18 instances of pericardial disease of which 9 were acute processes.

This was to be expected because in an acute rheumatic infection of the heart, the pericardium, myocardium, and endocardium are frequently all involved.

Summary and Conclusions. One hundred and forty-eight cases of rheumatic heart disease were studied to ascertain the cause of death. It was found that congestive heart failure accounted for only 33.1 per cent of the fatalities, acute rheumatic carditis for 23 per cent, peripheral emboli and thromboses for 11.5 per cent, subacute bacterial endocarditis for 29 per cent, and 3.4 per cent died of miscellaneous cardiovascular accidents like angina pectoris or acute pulmonary edema.

The groups of congestive failure and emboli and thromboses were the oldest, subacute bacterial endocarditis a little younger and acute rheumatic carditis the youngest.

Those that had aortic valvular disease alone were the oldest (52.5 years). The mitral cases came next (42.8 years) and the cases with combination of aortic, mitral and tricuspid were youngest (30 to 35 years).

There were more than twice as many females as males dying of acute rheumatic carditis, the relation was reversed in the group dying of emboli and thromboses and the proportion was 3 to 2 on the side of males in the subacute bacterial endocarditis group.

A past history of rheumatic fever or chorea was not found with equal frequency among the various groups. Although we believe that stenosis of any of the valves is, except in rare instances of congenital heart disease, practically invariably due to rheumatic infection, the multiform character of the early illness prohibits obtaining a positive past history in many instances. The greater the number of valves involved, the more frequently was a positive past history obtained. This is true for two reasons: such patients are more apt to have had more than one infection and they die at a younger age, so that the early illnesses are not forgotten. This explains why cases of aortic stenosis who die at an old age less frequently have a positive past history.

In speaking of valvular lesions in this review, except for those cases dying of subacute bacterial endocarditis, we mean stenosis to a greater or lesser extent. A striking finding was the great frequency of involvement of the aortic and tricuspid valves. When the tricuspid valve was involved, the mitral was always diseased as well, and frequently the aortic.

Auricular fibrillation was almost invariable in the emboli and thrombi group, very common in those dying of congestive heart failure, much less common in the acute rheumatic carditis group, and practically absent in those who died of subacute bacterial endocarditis. The presence of mitral stenosis is the most common accompaniment of auricular fibrillation, although this irregularity occurs occasionally in patients who have only aortic stenosis.

The average weight of the heart of those dying with congestive failure was 617 gm., of acute rheumatic carditis or emboli and thromboses about 550 gm., and of subacute bacterial endocarditis 449 gm. The average weight of the heart in cases of aortic stenosis was 669 gm., of mitral stenosis 474 gm., and of both 663 gm. When the tricuspid was involved in combination with other valves the average weight was about 550 gm. The presence of adhesive pericarditis increased the average weight by about 120 gm. The average weight of 43 cases with adhesive pericarditis was 654 gm., and of 62 cases with a normal pericardium was 534 gm.

Pericarditis with or without adhesions was less frequent in the older patients. It was most common in the group with acute rheumatic carditis, fairly frequent in those with congestive heart failure, and very rare with subacute bacterial endocarditis.

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PERORAL PULMONARY DRAINAGE.

NATURAL AND THERAPEUTIC, WITH ESPECIAL REFERENCE TO THE "TUSSIVE SQUEEZE."*

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IN presenting this subject we have no thought of making any comparisons between peroral and external surgical drainage of pulmonary suppurative foci; the decision as to the necessity for resorting to external surgery should be reached in the particular case by a consultation of the internist, or pediatrician, with the surgeon and, especially, the roentgenologist.¹ The findings of the bronchoscopist will often be helpful data at such a consultation.

Natural Peroral Drainage. Mucosal surfaces, even in health, must drain. The natural means for removal of normal as well as of

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pathologic pulmonary secretions are: (1) The cilia; (2) the bechic blast; (3) the tussive squeeze; and, possibly, (4) tracheobronchial peristalsis.

Ciliary Drainage. It is unnecessary, before a group of eminent internists, to go into the fundamental details of ciliary drainage. The important fact is that the cilia waft upward the secretions, normal and pathologic, to a point where these secretions can be blown out by the bechic blast.

Bechic Blast. Forcible expulsion of secretions by the bechic blast is limited to the larger tubes. There is no blast in the alveoli or bronchioles, and very little in small branch bronchi.

The Tussive Squeeze. This is the most powerful of all factors in natural peroral drainage. Yet it is the one apparently least considered. For instance, a number of eminent authorities on diseases of the lungs have stated that cough is inefficient because under pathologic conditions of bronchial obstruction air cannot get into the distal part of the lung, and consequently cough is powerless to force out the obstruction! This is a fallacy. The distal part, in fact, all of the peripheral parts of the lung, are emptied by the tussive squeeze. Another author stated that while it is certain that bronchoscopic aspiration is beneficial, its mechanism is mysterious because the aspirating tube cannot reach the periphery of the lung nor abscess cavities located therein. This author also ignores the tussive squeeze. In 110 articles in medical journals on closely related subjects, the authors give no evidence of a realization of the importance, or in many instances, even of the existence of the tussive squeeze. The tussive squeeze is the compression of the lung during cough. For purposes of illustration, a lobe of the lung may be likened to a sponge partially filled with water. When the sponge is squeezed, the water is forced out. Just so, when a lobe containing pus is compressed by the powerful bechic contraction, the pus or other fluid secretions are forced upward into the larger bronchi, whence they are removed by the bechic blast. It is not necessary that the lobe be solidly filled with pus; more or less air admixture is a help rather than a hindrance. The best simple illustration of the mechanics of the tussive squeeze is the florist's bulb sprinkler. It is partly filled with water; the florist compresses the bulb, the water is forced out; the florist does not immediately refill the bulb, he presses it repeatedly, each time forcing out some water that lingers notwithstanding the first squeeze; at each release of the bulb, air is drawn in, and as it is forced out fluid is carried with it. To continue the comparison, *the effect of codein on a patient trying to cough up pus might be compared to that of a drug paralyzing the florist's hand. The same may be said of the effect of phrenicectomy.*

Our first observations of the mechanism of the tussive squeeze were made through the bronchoscope; we see them repeated every working day. We aspirate all visible pus from the larger bronchi;

working with the cough reflex unhampered by any anesthetic, cough is frequent; it quickly forces up into view from the peripheral bronchi the pus they contain. Again and again this is repeated until the passages are emptied. There has been no necessity for putting either the bronchoscope or an aspirating tube down or out into the periphery of the lung; the pus is forced up into the large bronchi. It is thus objectively demonstrated that there are two separate and distinct mechanisms concerned in peroral drainage by the cough reflex, the bechic blast driving out the pus, and the tussive squeeze that brings up the pus to the large bronchi where the blast may complete the expulsion. The tussive squeeze is a powerful ally of the cilia in natural peroral drainage; and of the bronchoscopic aspirator in therapeutic drainage.

Inhibition of Natural Pulmonary Drainage by Viscosity. *Viscosity and Stagnation.* In doing bronchoscopy it is common to find quantities of thick, viscid secretion remaining in the lung after paroxysms of coughing, evidently secretions that the bechic blast could not expel.² When drawn out by a negative pressure of 4 or 5 pounds the viscosity is seen to be so great that the secretions will not run down in the glass collecting tube. This shows the viscosity of the newly formed exudate in the bronchi. The viscid, purulent secretion clings to the bronchial wall, resisting expulsion.

Air Bubbles and Mucus Lessen Viscosity. The to-and-fro movement of air with the phases of respiration lessens viscosity somewhat, especially when the mucous secretions are normal in quantity, as they may be if the glandular cells are not yet damaged by post-inflammatory changes, nor their activity inhibited by codein or atropin. The mucus serves as a lubricant if it is not thickened by inflammation or drugs. But in certain inflammatory conditions the viscosity of the secretions is enormously increased by an increase in fibrin.¹

The Bronchiectatic Septic Tank. The chief natural way of lessening viscosity is to rot the thick tenacious pus.² The saprophytic and other bacteria bring about this change just as they do in the contents of what the sanitary engineers call a septic tank.² In sanitation, thick sewage can be changed to a thin fluid free from specific bacteria by giving a place, temperature and sufficient time for saprophytic bacteria to bring about the change. The secondary pathologic changes in the bronchial walls are a fearful price to pay for lessening viscosity, however, and in fact constitute a strong indication for bronchoscopically aspirating the secretions before they have time to rot; thus we eliminate the bronchiectatic septic tank. Like Nature's amputations, the mortality attending lessening viscosity by septic tank methods is too high.

Inhibition of Natural Postural Drainage by Drugs. It has been pointed out^{3,4,5} that the cough reflex is the watch dog of the lungs, and that the indiscriminate giving of sedatives to lessen the cough

reflex is logically unsound and clinically pernicious. Nearly every medical graduate leaves school with the idea that cough, like hemorrhage, is a thing to be suppressed, and he has knowledge of the most powerful drugs that will suppress it.

Opium Derivatives have a doubly pernicious effect in inhibiting natural peroral drainage; in the first place, they check the cough, which is Nature's best method of expelling the pus laden with infective organisms; and, in the second place, opiates thicken the pus by checking the normal secretions that should thin it.^{3,5} "If the patient cough, give him codein" is a most pernicious order.

Incidentally, it might be mentioned at this point, that many forms of cough will yield symptomatically more quickly to other forms of medication than to sedatives; for instance, the harassing cough of influenza will yield to alkalization of tracheal secretion by internal administration of alkalies much more readily than to any sedative; and, moreover, the alkalization of tracheal secretions puts them into better physical state for expulsion.

Atropin is synergistic with opiates in inhibiting the production of serum and mucus that should thin the pus, therefore the routine, indiscriminate use of atropin is to be deprecated as theoretically illogical and clinically pernicious. Alone atropin is bad enough; combined with opiates it is worse; the combination becomes an ally of suppurative disease of the lung.^{3,5}

Inhibition of Natural Peroral Drainage by Operations. No one questions the usefulness of external drainage of suppurative foci in suitable cases of non-tuberculous pulmonary suppuration. No one questions the good results obtained by phrenicectomy and artificial pneumothorax in suitable cases of pulmonary tuberculosis, but there is much clinical evidence to show that in many cases of non-tuberculous suppuration, these two procedures, artificial pneumothorax and phrenicectomy, are alike in that they cripple natural peroral pulmonary drainage by annihilation of the bechic blast and the tussive squeeze. There is some bronchoscopic evidence to show that the efficiency of the cilia is also affected unfavorably by these procedures. We realize that both pneumothorax and phrenicectomy have a large field of usefulness, but we have seen so many patients made worse by both these procedures, that we would urge they be not applied to non-tuberculous pulmonary suppuration without the most careful consideration.

Therapeutic Peroral Drainage. Postural. This is a well known and important adjunct to medical care and management; there are few or no contraindications to its use. Its efficiency is very much less when the pus, or secretion, is of such high viscosity that it will not run downward when the collector is inverted;^{4,5} but this does not mean that it is altogether useless; even in such cases it helps.

Continuous Peroral Drainage. Moore⁶ perfected a means of inserting through the mouth and larynx a vertebrated metallic tube

to be left *in situ* continuously, or for long periods of time. It promises to be useful in some cases.

Bronchoscopic Removal of Obstruction to Peroral Drainage. Obviously, bronchial obstruction, when present, frustrates peroral drainage. The only way to determine the character of the bronchial obstruction is by diagnostic bronchoscopy and in most cases the only way to remove the obstruction is by means of instruments passed through the bronchoscope. Tumors, benign or even histologically malignant; compression stenosis; granulations; edema; fibrous stenosis; plugs of semisolid and crusted secretions; blood clots—all these conditions can be efficiently dealt with bronchoscopically with the restoration of a channel for peroral drainage.⁷

Bronchoscopic Aspiration. In peroral bronchoscopic aspiration we have the most powerful adjunct to medical care and management that has ever been discovered. The efficiency of the method has been demonstrated in so many thousands of cases, in the hands of so many different bronchoscopists, as to leave no room for doubt.

Medical Care and Management. Every patient bringing up pus from his lungs needs medical care and management. It is appalling to see the number of persons with productive cough who go about with apparently little thought by themselves or their family physician as to just what this symptom means. In a considerable percentage of the cases the patient could be cured by careful attention to diet, environment, and increased hours of rest in bed out-of-doors, along with careful attention to peroral pulmonary drainage.

Summary. 1. These observations were made with a view to an analysis of the factors concerned in (natural) peroral drainage. No comparisons are drawn between peroral and external surgical drainage.

2. Natural peroral drainage is by ciliary action, bechic blast and tussive squeeze. When bronchoscopy is done without abolition of the cough reflex by anesthesia on a patient with peripheral supuration it is always noted that, after the pus is bronchoscopically aspirated from the larger bronchi, fresh pus appears each time the patient squeezes the affected lobe by cough. This is repeated until the lobe is well drained of pus.

3. The tussive squeeze is naturally more or less intermittent, but it is vastly more efficient than ciliary action in dealing with pus of high viscosity.

4. Natural peroral drainage is inhibited by viscosity. Viscosity is lessened partly by permeation with air bubbles in the to-and-fro passage of air by the intermittent tussive squeeze, but chiefly by the "septic tank" process.

5. In the bronchiectatic septic tank, pus of viscosity too high to be expelled by the bechic blast, after it is brought up to the larger bronchi by the tussive squeeze aided more or less by ciliary action, is changed to thinner fluidity by putrefaction. This lessening of

viscosity enables expulsion by the bechic blast. The by-products of putrefaction are harmful to the bronchial walls so that, like Nature's amputations, the process is crude and the results leave much to be desired.

6. Promotion of peroral drainage is an essential aid to medical care and management in non-tuberculous suppurative diseases of the lungs.

7. Our observations lead us to believe that the best peroral drainage is obtained by attention to the following considerations: (1) Omission of drugs, like opiates and atropin, that inhibit the bechic blast, the tussive squeeze and the action of the cilia, or thicken secretions; (2) omission of operations like phrenicectomy, which also interfere with the bechic blast and tussive squeeze; (3) postural drainage (assisted to the utmost by the tussive squeeze), twice or three times daily, the patient selecting the times when he feels the greatest inclination to cough; (4) bronchoscopic clearance of all obstructions in the tracheobronchial tree at intervals of a week, more or less, according to indications. In the interim supplementary catheteric aspiration and medication may be carried out daily without the bronchoscope if desired.

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THE EFFECT OF PITUITRIN INJECTIONS ON BLOOD PRESSURE IN MAN.

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IN 1895 Oliver and Schäfer¹ reported a rise in blood pressure in anesthetized animals following intravenous injection of extracts of the pituitary gland. Three years later Howell² showed that this effect was due to the posterior lobe of the gland. This finding has since been confirmed by many investigators. But constantly

recurring in medical literature is the assumption that when injected intramuscularly into the unanesthetized human the same pressor action is obtained.

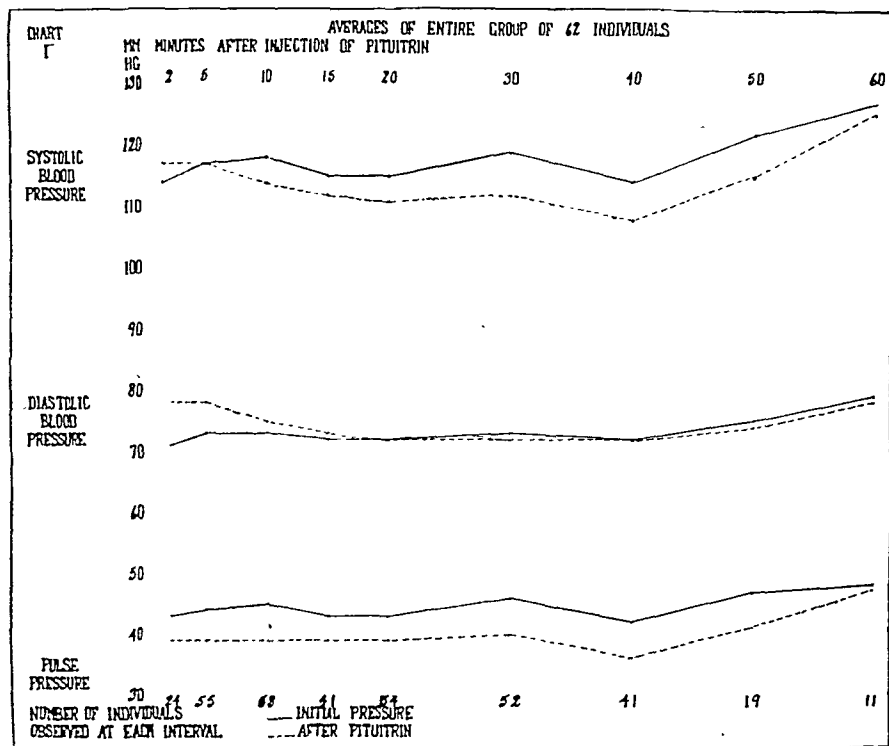
Yet as long ago as 1913 van den Velden³ said that he observed no constant and striking rise in systolic pressure after injecting therapeutic doses of pituitary extracts intramuscularly into man. A year later Behrenroth⁴ was unable to establish any definite and constant change in blood pressure following intravenous injections into man. In 1917 Schmidt⁵ published his results in a series of 15 febrile patients. He injected 1 to 1.5 cc. of pituitrin (Parke, Davis & Co.) intramuscularly and was unable to establish any constant effect on systolic pressure. He observed, however, that the diastolic pressure rose in the majority of cases, reading its maximum in 30 to 45 minutes and in some instances amounting to 15 mm. Hg. or more. In 1928 Ward, Lyon and Bemis,⁶ studying the comparative effects of oxytocin, "vasopressin" and pituitrin on obstetric cases after delivery, recorded the blood pressure at 3 intervals of 5, 10 and 15 minutes after intramuscular injection, and although they show a graph of a selected case with a rise of pressure following pituitrin, yet their graphs showing the average of 48 cases with 1 ampule dosage and 12 cases with 2 ampules dosage fail to show any significant change in pressure after pituitrin. They do not state how soon after labor the injections were made nor what anesthetics the patients were given.

The effect of anesthesia on the action of posterior pituitary extracts in animals has recently been brought to light. In 1929 Gruber,⁷ experimenting with the pressor fraction of pituitrin, "vasopressin," since renamed pitressin, found in dogs anesthetized with chlorotone a rise in pressure following intravenous injection, but in unanesthetized dogs, a fall. In a series of publications during the past 3 years from the Department of Pharmacology of McGill University,⁸ Gruber's results have been confirmed. In the most recent of these, published since the herewith presented investigation was completed, it is stated that their experiments "show conclusively that a fall in blood pressure is the predominating effect of the intravenous injection of pituitary extract in the normal unanesthetized dog." It is also suggested that the fall in pressure is due to constriction of the coronary bloodvessels which more than offsets the peripheral vasoconstriction tendency to raise the blood pressure.

In spite of this evidence the statement still stands in the latest edition of *New and Non-official Remedies*⁹ that "the intravenous or subcutaneous injections of preparations of the posterior lobe are followed by an increase in blood pressure which is maintained over a considerable period." And manufacturers of posterior pituitary extracts still often advise its use in patients with hypotension or in shock to raise the blood pressure, and still give hypertension as a contraindication to its employment.

Procedure. The present study was undertaken in order to determine whether or not there was any constant effect following the injection of posterior pituitary extract into man in the manner ordinarily employed and in the usual therapeutic dose. Obstetrical pituitrin (Parke, Davis & Co.) was injected deep into the muscle, the dose being 1 cc. Sixty-two patients of both sexes, ranging in age from 8 to 56 years, were employed. The initial systolic pressure ranged from 82 to 218 mm. Hg.; the initial diastolic from 58 to 110 mm. In all but a few cases the patients were given 0.3 cc. pituitrin (0) on the day before the test in order to eliminate so far as possible psychic effects and to guard against possible allergic reactions. The results are shown in the accompanying charts.

CHART I.



Results. Chart I shows the number of cases observed at intervals of from 2 to 60 minutes after injection of pituitrin, and the average pulse rate, systolic and diastolic blood pressure and pulse pressure of the cases observed at each time interval compared with the averages of this same group of individuals before injection. The systolic pressure averaged slightly higher only at 2 minutes after injection, was unchanged from the initial pressure 5 minutes after injection, but constantly thereafter and up to 60 minutes was

slightly lower than before injection. The diastolic pressure was somewhat higher at 2 and 5 minutes after injection and thereafter practically unchanged. The pulse pressure was somewhat decreased at all time intervals.

Chart II shows the percentage of rising, falling and unchanged pressures; also the greatest variations above and below the initial pressures, and the average rise or fall in pressure at each interval after injection. Slightly more than half of the patients showed a rise in systolic pressure 2 minutes after injection but thereafter the percentage rapidly diminished; at 30 minutes only 10 per cent were above the initial pressure. The diastolic pressure was raised in three-quarters of the cases at 2 minutes, but this percentage progressively decreased and, from 15 minutes on, more patients showed a fall than a rise. The greatest rise at any time in systolic pressure was 42 mm. Hg., and the greatest fall 44 mm.; in diastolic 24 mm. rise and 16 mm. fall. These figures were the exception. Few of the patients showed variations at any time of more than 2 mm. to 6 mm. The most suggestive figures are those in the average rise or fall tabulation. This again brings out the decreased pulse pressure following pituitrin injection, but this, except during the first few minutes, is brought about by a fall in systolic pressure.

CHART II.—NUMBER OF INDIVIDUALS OBSERVED, 62.

Time after injection:		2 min.		5 min.		10 min.		15 min.		20 min.		30 min.		40 min.		50 min.		60 min.	
	Unit.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.
Cases rising	%	54	75	47	73	27	55	27	44	26	37	10	40	17	37	21	37	18	27
Cases falling	"	33	8	29	18	60	34	61	49	67	44	69	46	73	51	74	47	64	55
Cases unchanged	"	13	17	24	9	13	11	12	7	7	19	21	13	10	12	5	16	18	18
Greatest rise	Mm.Hg.	40	22	28	16	18	16	16	16	20	16	26	16	42	24	12	8	42	22
Greatest fall	"	8	5	20	6	24	8	34	12	28	12	38	16	34	10	44	12	42	14
Average rise	"	3	7	0	5	..	2	..	1	..	0	0
Average fall	"	0	..	4	..	3	..	4	0	7	1	6	0	7	1	2	1

S = Systolic. D = Diastolic.

Chart III shows the averages in 13 patients with an initial systolic pressure of 100 mm. or below and Chart IV in 3 patients with an initial pressure of 198 mm. or higher. In Chart V the average rise or fall in the low and in the high blood pressure groups is shown in comparison with these averages in the whole group. In the hypotensive group the initial rise in systolic pressure was greater and longer sustained while the later fall was less; the diastolic was also higher in the early stages but its later fall was somewhat greater than was the case in the whole group averages. In the hypertensive group on the contrary the average systolic pressure was at no time higher than the initial pressure and from 10 minutes onward showed a marked fall; the diastolic was not so consistent, but in general after the 10 minute observation showed greater fall than in either of the other groups.

CHART III.

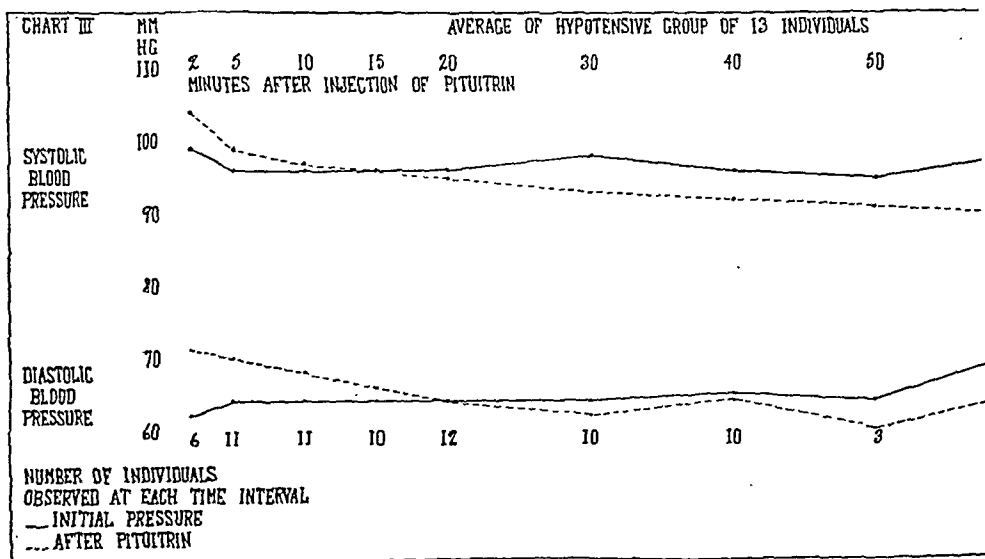


CHART IV.

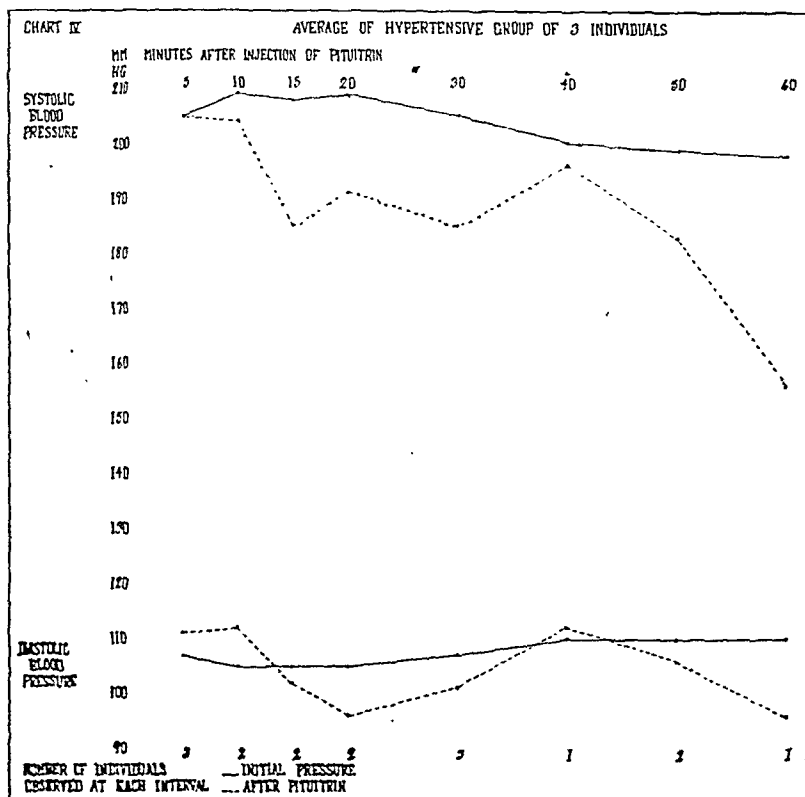


CHART V.—NUMBER OF INDIVIDUALS OBSERVED, 62.

Time after injection:		2 min.		5 min.		10 min.		15 min.		20 min.		30 min.		40 min.		50 min.		60 min.	
	Unit.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.
Whole group: Av. rise	Mm.Hg.	3	7	0	5	..	2	..	1	..	0	0
Av. fall	"	0	..	4	..	3	..	4	..	7	1	6	0	7	1	2	1
Low blood pressure: Av. rise . .	"	5	9	3	6	1	4	0	2	..	0
Av. fall	"	0	..	1	0	5	2	4	1	4	4	8	6
High blood pressure: Av. rise . .	"	0	4	..	7	2
Av. fall	"	0	..	5	..	23	3	18	9	20	6	4	..	16	4	42	14

S = Systolic. D = Diastolic.

Additional Observations. The average pulse rate showed a slight drop 2 minutes after injection in all groups, but the changes thereafter were so slight and inconsistent that they lack significance.

In 36 per cent of the patients the temperature rose slightly during the test, in 50 per cent it fell and in 14 per cent was unchanged. The average for the whole group, however, was 98.3° F., both before injection and at the end of the test period.

In 13 patients (21 per cent) there was an intestinal reaction, consisting of cramps, followed by a bowel movement. This occurred as early as 8 minutes after injection and as late as 60 minutes, averaging about 20 minutes.

In the hypertensive group no ill effects of any kind were observed. Two of the patients said that they felt better than usual at the end of the test period while the third, who was the individual showing the greatest drop in pressure, complained of a slight headache.

The fact that in the hypertensive group the fall in systolic pressure was so marked and so immediate as compared with the normal and hypotensive groups raises the question as to whether in these particular hypertensive individuals arteriosclerosis was more extensive in the peripheral vessels than in the coronary vessels and consequently the constriction produced by pituitrin comparatively greater in the coronary than in the peripheral vessels, whereas in those with normal bloodvessels the constriction was more nearly equalized. Further study of the effect of pituitrin on a larger group of hypertensive individuals is now under way and is being supplemented with electrocardiograms taken before and after pituitrin injection.

Summary. 1. One cubic centimeter of obstetrical pituitrin was given by intramuscular injection to 62 individuals and the blood pressure observed at 9 intervals of from 2 to 60 minutes.

2. No constant changes in blood pressure were observed.

3. In a few individuals there was a marked change in blood pressure, but this was as often downward as upward.

4. In the majority of individuals there was little or no change.

5. The general trend of the blood pressure was, except for a slight

transient rise immediately following injection, downward rather than upward.

6. This downward trend was more marked in the systolic than in the diastolic pressure resulting in

7. A slight but constant decrease in pulse pressure.

8. In general, the higher the initial pressure, the greater the fall following injection of pituitrin, and

9. The possible mechanism of this greater fall in hypertensive individuals is suggested.

Conclusions. 1. Intramuscular injection of pituitrin (1 cc. Parke, Davis & Co. obstetrical) into man is not followed by any constant change in blood pressure.

2. Where change is observed, it is more often a fall than a rise.

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STENOSIS OF THE PULMONARY CONUS AT THE LOWER BULBAR ORIFICE (CONUS A SEPARATE CHAMBER) AND CLOSED INTERVENTRICULAR SEPTUM. WITH TWO ILLUSTRATIVE CASES.*

**CASE 1. WITH DEXTROPOSITION OF AORTA AND ANEURYSM OF
INTERVENTRICULAR SEPTUM, ALL FETAL PASSAGES CLOSED.**

**CASE 2. WITH PATENT FORAMEN OVALE AND SUBACUTE INFECTIVE
ENDOCARDITIS.**

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A WELL-DEFINED but rather uncommon type of pulmonary stenosis is that in which the constriction is situated at the *lower bulbar orifice of the infundibulum*, which structure is expanded above,

* Presented before the meeting of the American Association of Pathologists and Bacteriologists, Washington, D. C., May 9, 1933.

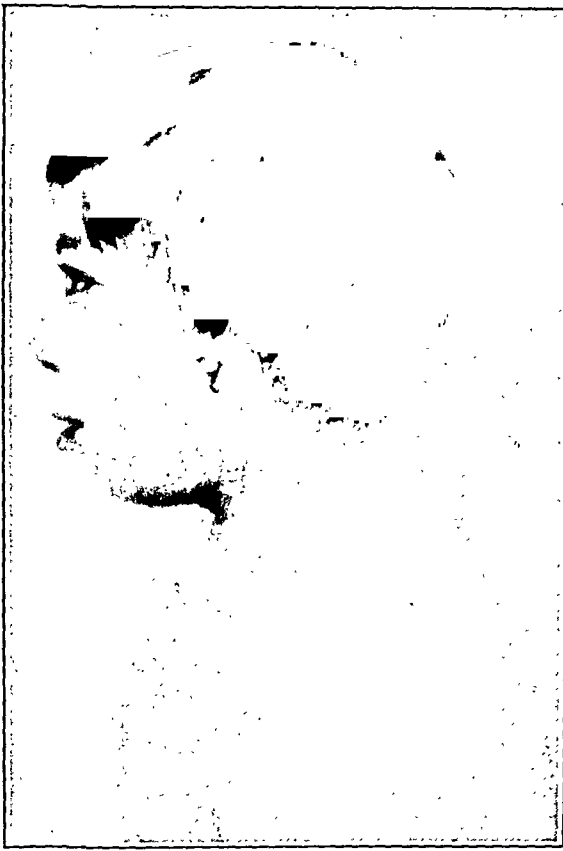


FIG. 1.—(Case 1.) Lateral view of head and upper part of body of patient showing vestiges of left auricle with slit-like canal opening and nodule of cartilaginous tissue at tip of mastoid, also abnormally low distribution of hair on the nape of the neck.

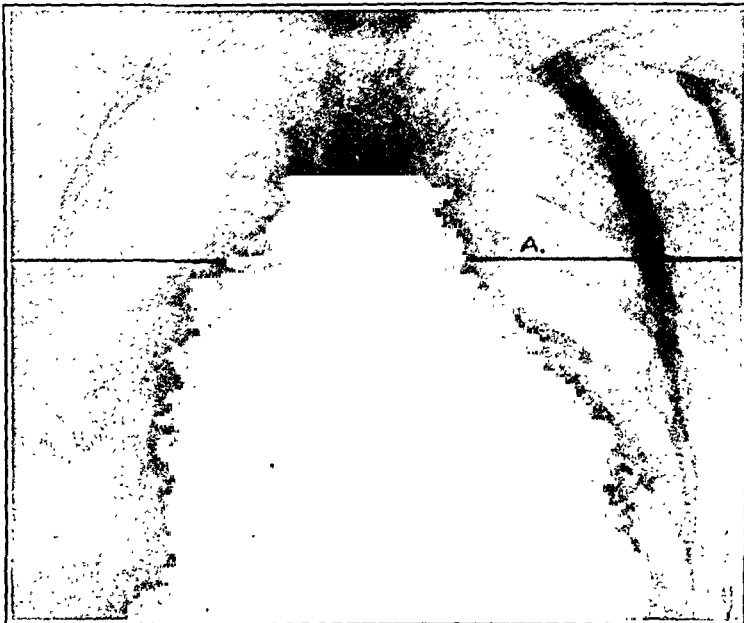


FIG. 2.—(Case 1.) Roentgen ray of heart showing great increase in transverse diameter due to dilatation of right auricle and marked hypertrophy of right ventricle, the latter forming the lower fourth of the right cardiac shadow. Broadening of the shadow to right in region of great vessels suggesting dilated superior vena cava and marked prominence of pulmonary arc due to dilated conus at A. The aortic knob is also prominent.

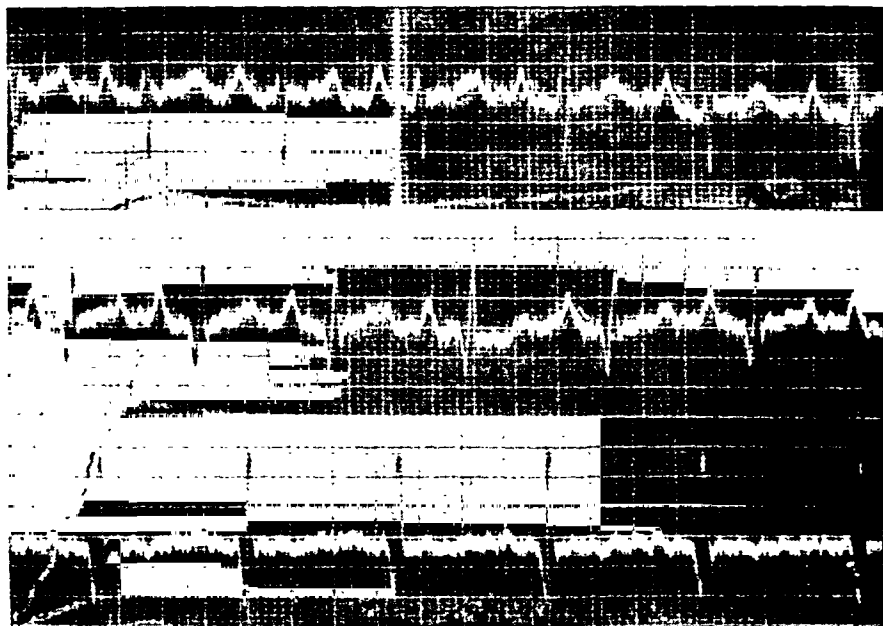


FIG. 3.—(Case 1.) Electrocardiogram showing right axis deviation and increased amplitude of Q.R.S. deflections. Large "P" deflections are seen in Leads I and II. The P-R interval is 0.24 seconds.

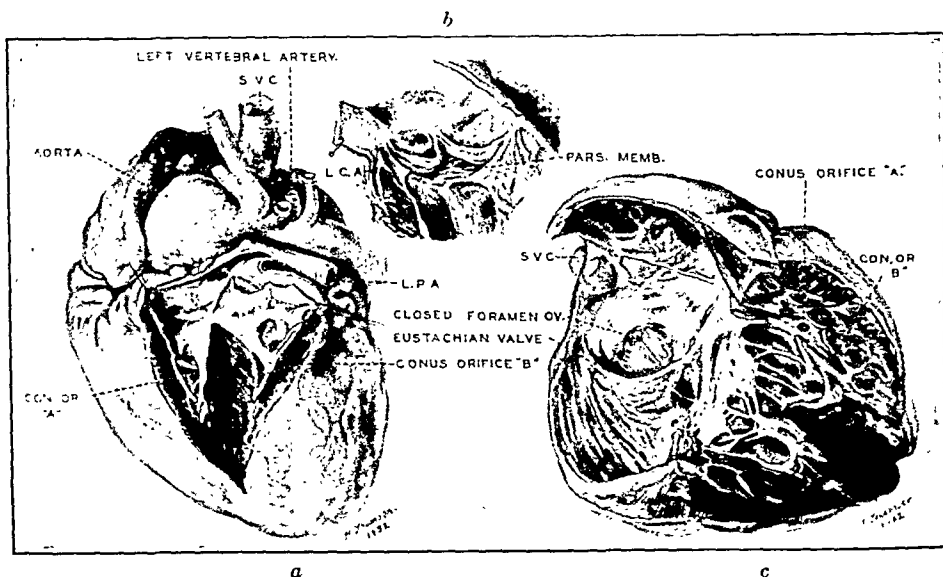


FIG. 4.—(Case 1.) Stenosis of pulmonary conus at lower bulbar orifice with complete closure of all fetal passages. *a*, anterior view of heart showing relations of great vessels at the base and the conus of right ventricle laid open. Note thickened endocardium lining triangular cavity and minute conus orifices communicating with sinus of ventricle also hypoplasia of pulmonary valve and trunk and dilated ascending aorta; *b*, interior of aortic vestibule. Note slight dextroposition of aorta and aneurysmal pars membranacea; *c*, right chambers laid open to show interior of sinus portion of right ventricle. Note massive simple hypertrophy and fibrosis of musculature of right ventricle and minute conus orifices, also anomalous chordae in right auricle. Specimen No. 10451 in the Medical Museum of McGill University. Drawing by Mrs. H. Thomson.

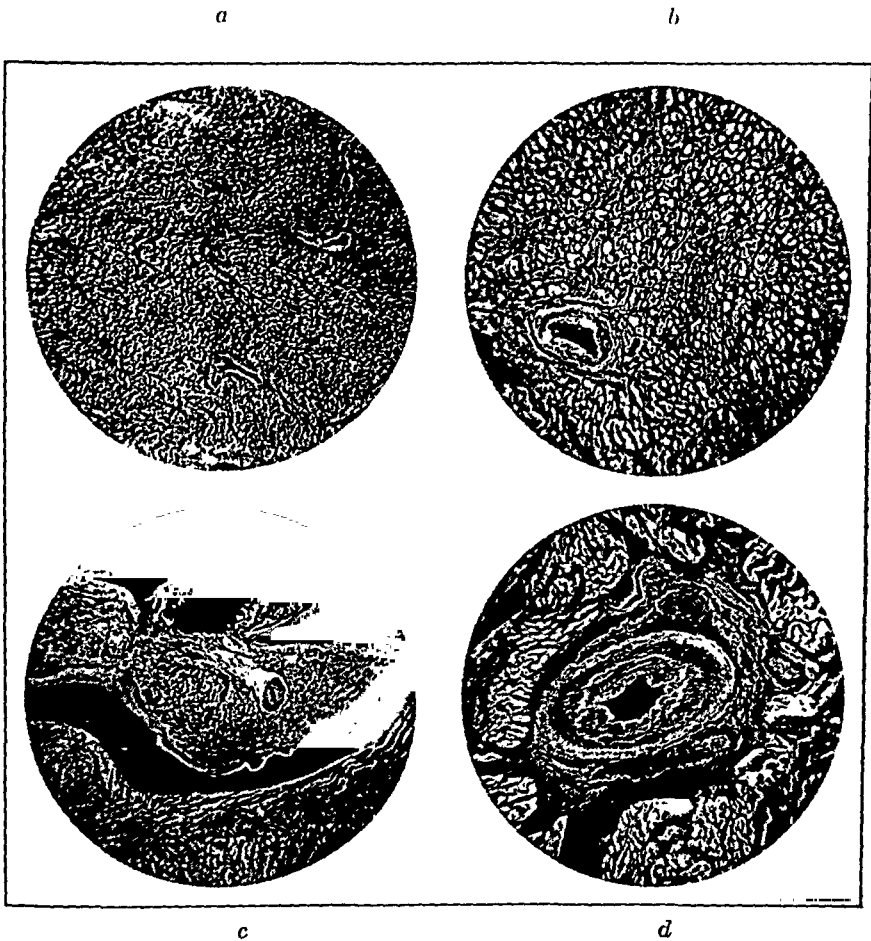


FIG. 5.—(Case 1.) Sections through myocardium of right ventricle in vicinity of stenosed bulbar orifice. *a*, low power view showing diffuse fibrosis of myocardium and sclerosis of vessels supplying fibrosed areas. Mallory's phosphotungstic; *b*, the same, high power view; *c*, the same showing curious asymmetrical hyperplasia of intimal lining of arteriole in fibrosed area; *d*, the same. Sclerosis of arteriole. High power. Elastic tissue stain.



FIG. 6.—(Case 2.) Roentgenograph of heart showing widening in region of right auricle, small aortic knob and some enlargement in region of pulmonary conus.

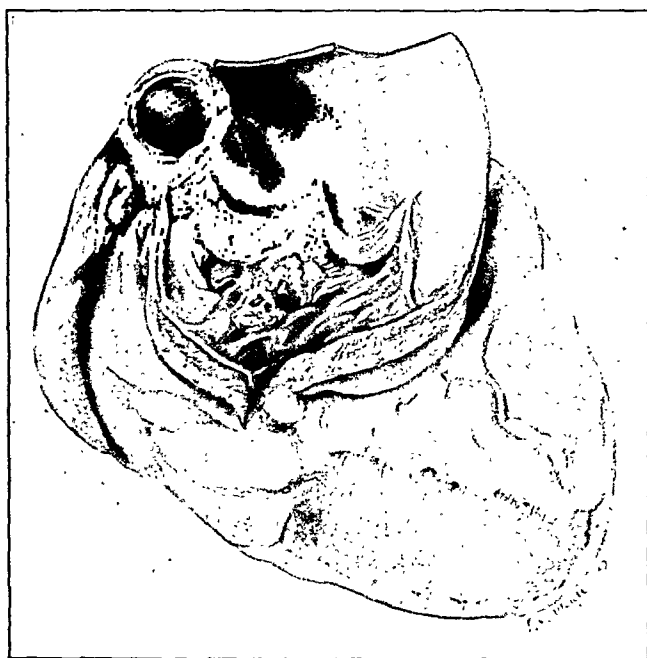


FIG. 7.—(Case 2.) Stenosis of pulmonary conus at lower bulbar orifice. Ventricular septum closed. Infective endocarditis (*S. viridans*) of pulmonary cusps and margins of conus orifice. Case of Dr. Wm. Thalheimer. Drawing by P. M. Larivière from the specimen in the Medical Museum of McGill University.

forming a separate chamber, from the distal end of which the pulmonary artery, usually unchanged in caliber and supplied with 3 normal semilunar cusps, is given off. This condition was first differentiated from other forms of pulmonary stenosis by Keith,¹ who found among 270 malformed hearts that he examined in the different London museums 19 instances of this anomaly. In his further study of the fate of the reptilian bulbus in the human heart he laid stress upon this type of malformation as indicating delayed involution or arrest of development of this structure at that early stage of embryonic life in which it exists as a separate cavity.

The bulbus cordis is that part of the primitive cardiac tube which lies between the common ventricle and the pulmonary aorta in the embryo between the 4th and 5th weeks of development. It represents a stage that is seen as a permanent condition in fishes, notably teleosts and elasmobranchs, and in certain reptiles. The fate of the bulbus, as pointed out by Greil, Keith and others, is incorporation into the musculature of the ventricles, with disappearance of its constituent on the left side, the blood passing here directly into the systemic aorta, while on the right side it persists as the infundibulum of the latter ventricle. Visible vestiges of the bulbus are seen in the adult heart in the great septal bands of the right ventricle and in the outer wall of the pulmonary conus. In the human heart the function of the incorporated bulbus is still, in the opinion of Keith and other anatomists, like that of Amphibia and Reptilia to provide a safeguarding of the capillary system of the lungs from raised and prolonged elevations in blood pressure. As the systolic pressure rises the valvular mechanism of the bulbus tends to shut off the pulmonary circulation. More recently, Spitzer has made the further suggestion that these cases as well as those of the so-called "tetralogy of Fallot" are explained by an incomplete torsion of the bulboventricular end of the primitive cardiac tube, which, he believes, leads secondarily to a persistence of the right "reptilian" aorta and to an obliteration of the so-called left aorta of the normal human heart. A discussion of this ingenious and fruitful theory is beyond the scope of the present article.

In most cases of stenosis at the lower bulbar orifice with persistence of the pulmonary conus as a separate chamber, a defect of the interventricular septum with some dextroposition of the aorta is associated, and this combination is to be expected, since normal involution of the bulbus takes place in early embryonic life before the cardiac septa have closed or normal torsion of the great trunks has taken place. The 2 cases here presented are of exceptional interest from this standpoint in that in both *the interventricular septum is closed*. In Case 2 (Fig. 6), there is no other associated anomaly except a widely patent foramen ovale, the interventricular septum being entire and the great trunks normally placed. In Case 1 (Fig. 4), however, a definite dextroposition and twisting upon itself of the aorta is present and there is also a distinct thin-

ning and aneurysmal bulging of the interventricular septum just anterior to the undefended space. Case 1 is further remarkable and, indeed, unique in the literature in that there exists here *complete closure of all fetal openings*, the foramen ovale and ductus arteriosus being both quite impervious and the interauricular and interventricular septa entire, in the presence of an almost complete obliteration of the lumen of the right ventricle between the sinus and conus at the situation of its "lower bulbar orifice." Thus the only avenues whereby venous blood could reach the lungs for aëration were the minute apertures in the musculature of this chamber described below (Fig. 4, orifices *A* and *B*). The result has been on the one hand an enormous ventricular hypertrophy behind the constriction with an extreme myocardial fibrosis and obliterative endarteritis of the coronary arterial radicles supplying the sclerosed areas; and on the other a hypoplasia of the otherwise well-formed pulmonary artery and valves, due to the small amount of blood transmitted to this vessel.

Where a defect of the interventricular septum is present, as in most of the cases of this type of conus stenosis in the literature, as also when other cardiac and grave somatic malformations were associated (as in our Case 1), a congenital origin of this anomaly may be safely assumed and Sir Arthur Keith's explanation of it as a delayed involution of the bulbus cordis with "persistence of the lower bulbar orifice" may be accepted as presenting at least a satisfactory hypothesis. In those cases, however, in which there is no defect of the interventricular septum nor any other cardiac anomaly except, as in Case 2 (Fig. 6), a widely patent foramen ovale, the question as to the possible inflammatory origin of the constriction in the lower part of the conus must be considered. The fact that histologic examination of the musculature of the right ventricle in this latter case showed no fibrosis or other evidence of old inflammation argues against such a contention, and for this and other reasons it seems to us probable that this also falls into the congenital category. An exhaustive search of the literature has revealed only 2 other cases of this type of bulbar stenosis without associated septal defect, those reported by Lafitte² and by Clarke.³ Both were in young women, aged 21, and in both the ventricular septum was entire and the foramen ovale widely patent. Clarke's case resembled our Case 2 in exhibiting extensive streptococcal vegetations. Following is the report of the 2 remarkable cases here presented:

Case Abstracts. CASE 1.—(From the Cardiac Service of the Children's Memorial Hospital.) *Stenosis of pulmonary conus at lower bulbar orifice, the conus forming a separate chamber with closure of all fetal openings and ventricular septum entire. Dextroposition of aorta with aneurysm interventricular of septum but no ventricular septal defect. Massive simple hypertrophy of right ventricle. Multiple somatic defects.*

A boy, aged 12, was admitted to the Royal Victoria Hospital on December 26, 1930, with a history of heart disease since birth. It was definitely

noticed that at 2 years of age, while running about and climbing stairs, he became very short of breath, cyanosed about the lips and tired easily. Though he did not take strenuous exercise or indulge in the usual games, he was considered to be in fair health until the present time. For 5 years he had been at an institute on account of his poor hearing and speech. About 2 weeks previous to admission, the principal had noticed that his appetite was poor, and that he was not as interested in his surroundings as usual. He next complained of general pain and malaise with some precordial pain, and 4 days later (December 24) it was noticed that his face was greatly swollen and that there was generalized edema of the body and scrotum. The condition had become progressively worse. There was no history of sore throat, nasal discharge or "cold" prior to the onset of edema. He had had a purulent discharge from both eyes intermittently since birth, more marked on the right. There was no past history of previous edema nor of rheumatic fever or chorea, convulsions, jaundice or hemorrhage. The tonsils and adenoids had been removed at 3. He was subject to "colds," and had measles at 6. His family history was negative; two brothers are alive and well.

Examination revealed marked edema of the face, lower sacral region and extremities; also ascites. He was very dyspneic, the lips, face, hands and fingers were moderately cyanosed and there was definite clubbing of fingers and toes. Temperature normal. There was a purulent discharge from both eyes with a *congenital papilloma of the right conjunctiva bulbi* at the limbus, which had incited a chronic conjunctivitis.

He had likewise a purulent discharge from both ears. There was also a *bilateral cleft of the hard palate*, not perforated. The soft palate was intact. His intelligence was somewhat below normal. There was also a congenital absence of both external ears (Fig. 1). The auricles were represented only by small nodules of cartilaginous tissue, on the right side located close to the opening of the meatus; on the left, more posteriorly just over the tip of the mastoid and 1 inch behind and above the slitlike canal opening. This opening existed on either side as a linear slitlike orifice, about $\frac{3}{8}$ inch from above downward. The canal itself was much narrowed as it extended inward and upward at an angle of 45 degrees; on the left side to 1 mm. in diameter and on the right to 2 mm. A probe could be passed on either side for a distance of $1\frac{1}{4}$ inches.

There was a marked increase in venous pressure: the jugular veins were engorged and showed visible pulsation. The pulse was regular, of small volume and there was no evidence of arterial thickening. Blood pressure was 92 mm. systolic and 70 mm. diastolic. Pronounced systolic thrill was present over the midprecordium, felt most strongly over the 3d and 4th interspaces at the left sternal border. At the level of the 3d rib the area of substernal dullness was increased. The heart was enlarged to 9.5 cm. to the left, 4.5 cm. to the right of the midsternal line. The sounds were well heard with a loud, rough, blowing systolic murmur of maximum intensity at the level of the 4th left interspace. It radiated from that point with diminishing intensity, being audible in the axilla and faintly in the back. The pulmonary and aortic second sounds were clear. Roentgen ray of chest at 6 feet (Fig. 2) showed the heart greatly enlarged both to right and left, with widening of the shadow in the region of the great vessels and a knoblike prominence of the pulmonary arch. The electrocardiogram is shown in Fig. 3.

Fluid was present at both the lung bases. The liver was greatly enlarged, but there was no definite pulsation. Ascites was present. The urine showed a specific gravity of 1022, a trace of albumin on admission only and occasional granular casts. The blood Wassermann was negative and the count showed R.B.C., 4,650,000; W.B.C., 8400; hb., 80 per cent.

He was discharged on February 20 to a convalescent home and read-

mitted on March 20. In the interval he had had recurring attacks of extreme cyanosis, but examination at this time showed the cardiac condition unchanged, though the enlargement of the liver had increased. On March 28 a fluoroscopic examination was made by Dr. Hugo Rösler, who reported as follows: "There is great enlargement of the heart to the right and left. The right contour is rounded, evidently produced by a dilated right auricle. The lung fields are clear and the pulmonary vessels at the hilum are not enlarged. The shadow above the heart is broadened, and there is a shadow along the left border suggesting a dilated superior vena cava (?)."

He was discharged from the Royal Victoria Hospital on March 28 and was admitted to the Children's Memorial Hospital on June 17. His condition was essentially the same, except that cyanosis and generalized edema were now extremely marked and he took little interest in his surroundings. By paracentesis of the abdomen 3000 cc. of fluid was withdrawn. The urine showed a specific gravity of 1015, but no albumin or sugar present. Examination of the blood showed the urea nitrogen to be 52 mg. per 100 cc.; creatinin, 2.22 mg. per 100 cc.; R.B.C., 5,500,000; W.B.C., 7400; hb., 80 per cent. He continued in this condition and died on July 9, 7 months after the sudden onset of circulatory failure.

Autopsy. (Children's Memorial Hospital.) There was extreme anasarca and a large accumulation of clear yellow fluid in the peritoneal cavity and left pleural sac. The lungs were collapsed and small, especially the left side, and the much hypertrophied heart occupied the greater part of the thoracic cavity (*vide infra*). The liver projected below the costal margin for 5 inches in the right mammary line, its surface was coarsely granular and the edge was thin as from long-standing passive congestion. It was densely adherent to the right abdominal wall by fibrous adhesions.

Microscopic examination showed passive congestion of the lungs, spleen and kidneys and advanced cardiac cirrhosis of the liver, cloudy swelling of the kidneys and an old perisplenitis with degeneration and fibrosis of adrenals.

Detailed Description of Heart. (M. E. A.) (Fig. 4.) *Appearance in situ:* The heart lay almost transversely in the thorax with the huge ventricular part next to the diaphragm. The greatly dilated right auricle arose perpendicularly on the right to a height of 6 cm. above the *a-v* groove, encircling the large aorta on the right and its auricular appendage, and curving forward anteriorly to the median line. A very deep *a-v* groove separated the muscular shoulder of the right ventricle from the right auricle and the root of the right auricular appendix. In the depth of the hollow so formed was seen arising in the median line a very large arterial trunk, the aorta, which was elongated in the ascending and first part of the transverse arch, and, bulging to the right, turned sharply to the left and gave off from the left upper angle of the transverse arch the great vessels in their normal relations but crowded together. An anomalous artery (? left vertebral) arose between the left carotid and subclavian. In front and to the left of the aorta was the prominent elevation seen in the Roentgen ray which proved to be the collapsed and thin-walled dilated conus of the hypoplastic pulmonary artery.

On laying open the heart the huge *right auricle* was seen to have hypertrophied walls 0.5 cm. thick. The Eustachian valve, guarding the I.V.C. orifice, was a large semilunar structure, 3 cm. long by 1.3 cm. wide, and presented a curious reticulated structure, but not fenestrated. The Thebesian valve was represented by a fine cord crossing the coronary sinus from the lower edge of the Eustachian valve to the tricuspid orifice, which sent off from its center a single branching filament inserted by two attachments to the posterior borders of the coronary sinus orifice. Another anomalous chorda, 3 cm. long, crossed the cavity of the right auricular

appendix from above downward to be inserted in the wall of the right auricle about 1 cm. above the marginal tricuspid segment. The foramen ovale was completely closed and the annulus ovalis well formed.

The *right ventricle* possessed an enormously thick wall, 2.5 cm. in parts, with a small cavity and much hypertrophied columnæ carneæ. The endocardium was greatly thickened. The conus at first appeared to be completely separated from the sinus by the heavy muscular trabeculæ forming the thick anterior wall of the latter. Closer observation, however, disclosed a small ovoid foramen with tendinous edges, 5 cm. in its longest diameter, situated in the anterior wall of the ventricle, 2 cm. below the junction of the septal and infundibular tricuspid segments and 3 cm. from the apex. This orifice perforated the musculature and led into the lower angle of the conus, which thus formed a triangular and entirely separate chamber with the apex directed downward, 2.5 cm. in depth and 4.5 cm. in circumference at its base, just below the pulmonary valve where it burrowed some distance into the musculature to the right and anteriorly. The walls of this conus chamber were 1 cm. thick and lined by thickened endocardium, differentiated at its lower angle into some fine strands resembling chordæ tendinæ which were attached to the margins of two minute channels leading downward between the trabeculæ and emerging into the sinus of the right ventricle near its apex. The pulmonary cusps, 3 in number, were smaller than normal and inserted abnormally deep in the musculature of the conus, but thin and healthy. The pulmonary orifice was 3.5 cm. in circumference and without constriction or stenosis, but both it and the artery were distinctly hypoplastic, the latter being very thin-walled and only 3 cm. in circumference. The ductus arteriosus was entirely closed, a faint scar on the interior of the aorta opposite the origin of the left subclavian artery remaining to mark its site of obliteration there.

The *left auricle* was a roomy chamber, about half the size of the right, lined with thickened endocardium, and walls somewhat hypertrophied (0.5 cm. thick) but was otherwise normal. The mitral valve and orifice were normal in size and appearance. The *left ventricle* was small in comparison with the right, with walls 1 cm. thick. The aorta was thick-walled and some 4 cm. in circumference. It was twisted on its axis and dextroposed to the right, its left anterior cusp being apposed posteriorly to the right posterior pulmonary cusp with its right anterior and posterior cusps entirely to the right of the pulmonary artery. The undefended space was large, with its anterior border below the junction of the left anterior and posterior aortic cusps. The interventricular septum was closed, but the area just anterior to the undefended space was membranous, indicative of a defective development. At this area it bulged forward and downward into the right ventricle just at the junction of the septal and infundibular cusps of the tricuspid valve, forming a channel which ended blindly behind the thickened endocardium lining the sinus, 2 cm. above the conus orifice.

A *histologic study of the myocardium* of the right and left ventricles was carried out with the kind assistance of Dr. L. J. Rhea, pathologist to the Children's Memorial Hospital and the following interesting findings were described:

Right ventricle (longitudinal section taken from the attachment of the tricuspid valve to the apex through the entire thickness of the posterior wall): The endocardium shows some localized areas of thickening and fibrosis. There is a general increase of connective tissue throughout the myocardium and in addition there are numerous focal areas of fibrosis which vary in extent from a moderate degree to one which almost completely replaces the musculature. In these patches of extreme fibrosis the surviving muscle fibers show marked atrophy (Fig. 5, *a, b*). The fibrosis has no fixed relation to any particular area of the myocardium but is more marked in the region subjacent to the endocardium, extending inward for

some distance beneath this and gradually fading away in the surrounding musculature, and it is most extreme toward the apex and in the vicinity of the abnormal "bulbar" orifice. The muscle fibers in the areas relatively free from fibrosis show hypertrophy and some degeneration.

Vascular changes: Associated with the focal areas of fibrosis in the myocardium is a marked degree of sclerosis of the coronary branches supplying the part. This sclerosis is much less pronounced in the less fibrosed areas but reaches an extreme degree in the arterioles that supply that part of the myocardium described above as being the seat of the most advanced connective tissue replacement. In some arterioles the sclerotic change involves the entire circumference of the vessel, the lumen of which is almost obliterated; in others this is limited to one side of the arterial wall (Fig. 5, c). One of the vessels that presents the most marked lesions is situated just beneath the endocardium and is separated from this on either side by thin trabeculae of muscle bundles (Fig. 5, d).

The pericardium is thickened in some places and one area of intense fibrosis with a small sclerosed artery in its center is seen. On the whole, however, it shows relatively little change.

Left ventricle: The myocardium is relatively normal, only a slight degree of fibrosis being present. The arterioles are likewise normal except in the case of a few isolated branches possibly derived from the right coronary circulation, which show a moderate degree of intimal thickening.

Interventricular septum: Sections taken at the base in the region of the bundle of His show the same extensive fibrosis of the myocardium directly underlying the endocardium on the side of the right ventricle and undoubtedly some of the fibers passing down in this situation must have been caught in this scar tissue, thus accounting for the slight delay in conduction present during life, but the area where this had occurred was not made out in the sections. On the side of the left ventricle, on the other hand, and in the deeper layers of the right ventricle, the muscle fibers were intact and there was little or no fibrosis.

CASE 2.—Stenosis of pulmonary conus at lower bulbar orifice (conus a separate chamber), ventricular septum closed, foramen ovale widely patent. Subacute bacterial endocarditis of pulmonary cusps and margins of conus orifice and embolic glomerulonephritis. Terminal cyanosis.

The heart from this case was presented to one of us (M. E. A.) for the McGill Museum by Dr. William Thalheimer of Milwaukee, Wis., whose account of the autopsy is transcribed below. The following clinical notes were kindly supplied by Dr. H. A. Holbrook of that city.

The patient was a young married woman of unstable family history. One sister committed suicide, another had been in a sanatorium for 20 years with paranoia, a third had pernicious anemia and one brother is hypochondriacal and a confirmed neurasthenic. Three other sibs were alive and well. Both parents died following a cerebral thrombosis, aged respectively 75 and 79; in both the blood Wassermann was negative.

Personal History. "The patient had suffered no illness of significance. Examining her before her projected marriage, I discovered a heart lesion which was manifested by an atypical very loud blow with maximum intensity over the pulmonary valve area, but extending over the precordial region and being audible over almost any part of the chest to careful auscultation. The diagnosis of disease of the pulmonary orifice was made, and the patient advised against pregnancy. The family dissented; had never had any intimation that this daughter had ever had any heart affection and took her to see Dr. Frank Billings in Chicago. Dr. Billings made a diagnosis of probable pulmonary and possibly aortic affection and advised against pregnancy. This advice was not heeded, and, following upon her marriage, she went through 2 pregnancies with an almost fatal outcome to her each time. The 2 children were apparently perfectly normal.

After each delivery she spent at least 2 months in bed, and after 1 spontaneous miscarriage at about the 5th or 6th month she was in bed some 3 months.

"During my observation of her, which extended from the discovery of her trouble until the day of her death, she showed dyspnea on exertion which increased in her later days to the extent of fainting spells and a cyanotic appearance. Early in her married life she played golf and tennis and rode horseback. Later she could not carry on these activities. I noticed no clubbing of her nails. Her blood Wassermann and Kahn tests were consistently negative.

"Roentgen ray of her heart taken a few months before death (Fig. 6) showed a heart of unusual shape with considerable widening in the region of the right auricle and in the region of the pulmonary artery. On the other hand, the aortic knob is very small for a heart of this size. The appearance is rather characteristic of congenital heart disease.

"The blood cultures before death showed consistently greenish colonies of chains of Gram-positive cocci—characteristically *streptococcus viridans*."

A *partial autopsy* was done on October 19, 1927, by Dr. Thalhimier. Inspection showed a considerably emaciated body with skin of a peculiar creamy gray (so-called *café-au-lait*). The peritoneal surfaces were smooth and glistening and there was no free fluid in the abdomen. The liver was somewhat enlarged and presented marked nutmeg appearance and a considerable degree of cloudy swelling. The spleen was about twice its normal size, soft, with tense capsule and bulging out surface, but no infarcts. The lungs presented large areas of gray hepatization in the lower lobes of both lungs but no infarcts and there were firm pleuritic adhesions of the lower right lung and the apex of the left. There was no fluid in either pleural cavity.

The *heart* (Fig. 7) was slightly enlarged, but lay in its normal position. The pericardial cavity contained 50 cc. of serofibrinous fluid. Both visceral and parietal pericardia were cloudy and covered with creamy yellow fibrin. The heart measured from base to apex 12.5 cc. The wall of the right ventricle was 1.5 cm. thick from base to apex. The left ventricle had the same thickness also from base to apex. The right auricle was moderately dilated, its wall slightly, if at all, thickened and its lining somewhat whiter than normal. The auricular appendage was normal. The tricuspid orifice admitted 3 fingers, its flaps were slightly thickened and fibrosed, and their auricular surface somewhat irregular. There were no vegetations upon it, and no projecting shelf. The trabeculae of the right ventricle were very large and prominent. There was a very unusual anomaly of the outflow tract of the right ventricle, with obscure orifice. At the base of the ventricle where the ventricular wall was reflected from the interventricular septum, and lying immediately behind the insertion of the tricuspid valve, was a small, irregular opening, 8 mm. in its longest diameter and 4 mm. in width, having the appearance of an irregular slit. Its edges on the ventricular side were very white and fibrosed, and completely covering this edge and covering the slit as it proceeded away from the ventricle were greenish, yellowish, wartlike, friable vegetations, which projected only a few millimeters. The pulmonary artery was then opened from above downward. As soon as this was opened it was found to contain a large, irregular, greenish-yellow thrombus, about 1.5 by 1 by 5 cm. in size, attached to one of the pulmonary cusps, but otherwise lying free. The incision, continued beyond the pulmonary cusps until it came to the slit previously described, revealed a normal pulmonary ring, with 3 cusps, all of them showing polypoid and warty vegetations of the type already described. The large vegetation found in the pulmonary artery was found to have its base attached to the most anterior of the pulmonary cusps, and lying upon the pulmonary cusp next to that on which it arose. This last

pulmonary cusp was almost completely eroded away, its irregular edge showing fine, wartlike vegetations. Below the pulmonary ring is a small muscular cavity, 3 cm. in depth and about the same in width. It went downward to an apex, to one side of which can be seen the superior opening of the slit already described. This view of the slit was similar in appearance to that seen from the ventricular side, but this edge is surrounded by more and larger vegetations, which extend on to the wall of this cavity for a distance of 0.5 cm. around the edge of the slit. The wall of this muscular cavity at its thickest portion was 0.5 cm. thick. The course of the blood, therefore, was from the right ventricle through this narrow opening into this small extramuscular chamber, and from there into the pulmonary artery. The left ventricle shows no special abnormality. The left auricle is about normal in size, and the mitral flaps are a little more thickened and irregular than the tricuspid ones. The outflow tract leading into the aorta is normal. The aortic valves, seen from above, appeared to be slightly, irregularly thickened, but showed no vegetations or other marked abnormality. The foramen ovale was closed. The coronary arteries could not be carefully investigated, but seemed to show no abnormality.

Microscopic examination showed marked hyperplasia of the fibers of the right ventricle and considerable fragmentation, but no definite areas of fibrosis or marked changes in the bloodvessels. The *left ventricle* presented a much slighter and more irregular hyperplasia of the muscle fibers and some perivascular round cell infiltration. The *kidneys* presented a few definite embolic glomerular lesions and some focalized areas of round cell infiltration, tubules distended with albuminous material and hyalin casts and a diffuse increase of interstitial tissue. *Spleen* showed marked congestion and hyperplasia with hyalinization of Malpighian corpuscles. *Liver*, marked cloudy swelling and fatty degeneration. Gray hepatization and edema of lungs.

Remarks. One of the most interesting features in the remarkable heart of Case 1 is the extensive myocardial degeneration and fibrosis of the wall of the right ventricle proximal to the constricted conus orifices and the extensive sclerosis with intimal hyperplasia of the coronary arterioles in this location. Neither the conus of the right ventricle distal to the defect nor the wall of the left ventricle presented these degenerative and sclerotic changes, which were sharply localized to the sinus of the right ventricle and were undoubtedly the indirect result of the greatly raised pressure in this chamber, which had to force all the blood for the pulmonary circulation through these two minute openings (Fig. 4, *a, b*) all fetal passages having become closed so that no other outlet existed. The sequence of events as regards the localized coronary sclerosis is not obvious, for since the right coronary arose normally from the aorta and the systemic blood pressure remained within normal limits, a rise of pressure within the cavity of the right ventricle could not act upon the pressure within the right coronary lumina. However, the following tentative explanation may be offered: The first response to the strain thrown upon this chamber by the force required for the expulsion of the venous blood to the lungs was clearly the development, at an early stage and while the right coronary branches were healthy, of the extraordinary degree of simple hypertrophy of this chamber that existed (its walls being

2.5 cm. thick). A certain amount of myocardial degeneration and fibrosis might well have accompanied and followed this extreme hypertrophy, but this would not in itself explain the coronary sclerosis. At the same time, however, the effects of the friction of the impeded blood current upon the endocardium of the small sinus chamber behind the conus orifices must have been greatly intensified by the abnormally high pressure that existed here, resulting in a marked thickening and fibrosis of the endocardium here and extension of these changes to the immediately underlying myocardium. This conclusion is borne out by the fact that this myocardial degeneration was definitely more pronounced in the vicinity of the defect and toward the interior of the ventricle than toward its epicardial surface. The extraordinary change that supervened in the coronary radicles suggest that the terminal radicles of these may have become involved in this fibrosis with resultant constriction of their lumina and that a *raised peripheral pressure* in these areas resulted. A vicious circle would thus have been created, the coronary sclerosis exaggerating the fibrosis, and the progressive advance of the latter increasing always more and more the peripheral resistance by involving new areas in the sclerosing process. This seems to us the most reasonable explanation of the changes shown in Fig. 5, *a, b, c, d*.

In Case 2, on the other hand, the constriction at the lower bulbar orifice was of quite as severe a grade but the foramen ovale was widely patent, permitting free escape of the blood dammed back behind the stenosed orifice into the left auricle. The result was that the same condition of raised pressure did not exist in this case in the sinus of the right ventricle, so that, although there was some little hypertrophy of the muscle fibers in this situation, there was practically no myocardial degeneration or fibrosis, and the extraordinary sclerosis of the coronary arterioles seen in this locality in Case 1 was here entirely absent.

The other feature of special interest in this second case lies in the presence, on the pulmonary cusps and margins of the bulbar orifice in its conus side, of a luxuriant growth of subacute bacterial vegetations of *Streptococcus viridans* origin. So abundant was this process that a large tag, attached to one pulmonary cusp and necrosing another across which it lay, projected free into the pulmonary artery for a distance of 5 cm. (not shown in Figs. 5 or 6, as it was unfortunately torn off and lost before the drawing was made). The valvular endocardium elsewhere alike at the tricuspid, mitral and aortic orifices was free from disease. The frequency with which a *Streptococcus viridans* infection involves the seat of a cardiac anomaly in patients attaining adult life is notorious and Thalheimer's case is a classic example of this combination.

Summary. 1. Two cases are presented of stenosis of the pulmonary conus at the lower bulbar orifice, in both of which the interventricular septum was *closed*. In Case 1 all other fetal passages

were closed also and a remarkable condition existed of localized degeneration and fibrosis of the myocardium of the right ventricle behind the stenosed orifice together with sclerosis of the coronary arterioles supplying the musculature in this area.

2. This localized sclerosis and myocardial degeneration would appear to have been an indirect result of the tremendously raised pressure that existed in this case in the interior of the sinus of the right ventricle, the wall of which, owing to the closure of all fetal passages, had to force all the blood required for the pulmonary circulation through the constricted conus orifice. This abnormally high pressure is thought on the one hand to have produced an extreme degree of simple hypertrophy with some accompanying myocardial degeneration, and on the other hand to have increased the effects of the attrition exercised by the impeded blood current on the endocardium lining the chamber behind the defect, this friction under pressure producing a fibrosis extending from the endocardium in the vicinity of the defect to the subjacent myocardium. It is suggested that the myocardial fibrosis thus induced would have so involved the terminal coronary arterioles that a localized condition of *raised peripheral pressure* resulted. In this way a vicious circle was created, the end-result being the remarkable obliterative coronary sclerosis with myocardial degeneration of the areas supplied.

3. In Case 2 a widely patent foramen ovale coëxisted with the defect and this relieved the pressure in the local circulation behind the constriction. There was no sclerosis either in the coronary vessels in this situation nor in the myocardium supplied by these, although the patient had attained adult life and had been through 2 pregnancies.

4. Case 2 adds to the literature another instance of a subacute *Streptococcus viridans* infection developing at and sharply localized to the seat of a cardiac anomaly. It also illustrates the extraordinary luxuriance on the side of the right ventricle of the vegetations so induced, a feature the peculiar significance of which is not yet fully understood.^{5,6}

The writers' thanks are expressed to Dr. L. J. Rhea, pathologist to the Children's Memorial Hospital, for his assistance in the histologic studies made upon the myocardium of Case 1; also to Dr. William Thalheimer and Dr. H. A. Holbrook, of Milwaukee, Wis., for so kindly placing at our disposal the clinical and pathologic data of Case 2.

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REVIEWS.

ASTHMA, HAY FEVER AND RELATED DISORDERS. By SAMUEL M. FEINBERG, M.D., F.A.C.P., Assistant Professor of Medicine and Attending Physician in Asthma and Hay Fever Clinic, Northwestern University Medical School; Attending Physician, Cook County Hospital, Chicago. Pp. 124, 8 illustrations. Philadelphia: Lea & Febiger, 1933. Price, \$1.50.

THIS little volume is a statement for laymen of the theory and principles of diagnosis and treatment in the allergic diseases. Without going into very great detail, it nevertheless will give the patient a better understanding of his ailment and thereby make possible intelligent coöperation on his part.
R. K.

MEDICAL ASPECTS OF OLD AGE. By SIR HUMPHRY ROLLESTON, BART., G.C.V.O., K.C.B., M.D., HON. D.Sc., D.C.L., LL.D., Regius Professor of Physics in the University of Cambridge, etc. Pp. 205; 7 illustrations. New York: Macmillan & Co., Ltd., 1932. Price, 7/6.

A REVISED and enlarged edition of the Linacre Lecture of 1932, this little volume is not a treatise on geriatrics, but an interesting presentation of various medical phases of the subject that will provide instructive and pleasant reading for all physicians.
R. K.

INDIVIDUALITY OF THE BLOOD. By PROFESSOR LEONE LATTES, Director of the Institute of Forensic Medicine in the University of Modena. Translated by L. W. HOWARD BERTIE, M.A., B.M., B.CH. (OXON.), from the French Edition, 1929. Pp. 413; 71 illustrations. New York: Oxford University Press, 1932. Price, \$7.50.

A DISCUSSION of "those constitutional peculiarities of the blood which enable us to distinguish between individuals of the same species." The author presents an exhaustive review of data on human isoagglutination and isolysis; the hereditability of these characteristics; the clinical application in such procedures as transfusion and tissue grafting; the medico-legal aspects (determination of parentage, diagnosis of blood stains); techniques of the various tests. That the author has performed a great service in assembling under a single cover an enormous amount of information that hitherto could be found only in isolated articles (2375 references in 92 pages of bibliography) is attested by the fact that the volume has been translated from the original Italian into German, French and English.
R. K.

NON-TROPICAL SPRUE. By TH. E. HESS THAYSEN, M.D., Senior Physician to the St. Elizabeth's Hospital, Copenhagen. Pp. 258; 39 illustrations: Copenhagen: Levin & Munksgaard, 1932; London: Oxford University Press, 1932.

THE author presents in detail all available data in the 34 cases (including 7 of his own) of non-tropical sprue that has been reported in the medical literature. On an analysis of this material he bases the conclusion that non-tropical sprue, tropical sprue and coeliac disease (intestinal infantilism) are very nearly related, probably identical conditions. The evidence is well presented and the argument convincing. An important original observation of the author is the finding of low or normal blood sugar curves on glucose feeding in non-tropical sprue, as contrasted with the usual finding of high figures in pancreatic steatorrhea, a condition with which non-tropical sprue may be confused.
R. K.

A SYSTEM OF BACTERIOLOGY IN RELATION TO MEDICINE. VOLUME VI—IMMUNITY. By VARIOUS AUTHORS. Pp. 537; various charts and tables. London: Medical Research Council, 1931. Obtainable in the United States at the British Library of Information, 5 East 45th St., New York. Price, 1/1/9; for the set 8/14/9.

THIS book continues the standard set by the preceding volumes of this series published under the auspices of the Medical Research Council. Of particular interest are the chapters on the natural immunity and active immunization with toxin. The chapter on anaphylaxis and related phenomena is particularly well rounded and endeavors to discuss this subject on the basis of recent advances in physiology. Pertinent references to the literature are placed at the end of each chapter. An addition such as this to a system of bacteriology should be distinctly valuable to the immunologist and to the clinician.

L. C., JR.

PHYSICAL THERAPY. By JOHN S. COULTER, M.D., Assistant Professor of Physical Therapy, Northwestern University Medical School, Chicago. Vol. VIII of Clio Medica Series, edited by E. B. KRUMBHAAR, M.D. Pp. 142; 15 illustrations. New York: Paul B. Hoeber, Inc., 1932. Price, \$1.50.

AN absorbingly interesting and scholarly presentation of the history of physical therapy. This volume maintains the high standard of its predecessors in the series.

G. W.

THE DIAGNOSIS AND TREATMENT OF POSTURAL DEFECTS. By WINTHROP MORGAN PHELPS, B.S., M.D.; M.A., F.A.C.S., Professor of Orthopaedic Surgery, Yale University, etc., and ROBERT J. H. KIPHUTH, Assistant Professor of Physical Education, Yale University, etc. Pp. 180; 107 illustrations, 14 tables. Springfield, Ill.: Charles C Thomas, 1932. Price, \$4.00.

A WELL written, well illustrated and well printed monograph upon a much needed subject. It should have wide use, not only among physicians, but also among physical educators and others interested in body mechanics.

G. W.

SOME FACTORS IN THE LOCALIZATION OF DISEASE IN THE BODY. By HAROLD BURROWS, C.B.E., F.R.C.S., Assistant at the Research Institute of the Cancer Hospital (Free), Consulting Surgeon to the War Memorial Hospital, Gasport, etc. Pp. 299; 6 figures and 8 colored plates. New York: William Wood & Co., 1932. Price, \$4.50.

ISOLATED clinical observations and experimental facts are gathered from numerous sources and woven into a treatise which stirs the imagination of the reader. For the thoughtful, the volume is replete with ideas. It opens new vistas; it stimulates.

G. W.

FOOD, NUTRITION AND HEALTH. By E. V. MCCOLLUM, Ph.D., Sc.D., and J. ERNESTINE BECKER, M.A., Professor and Associate, of Biochemistry, School of Hygiene and Public Health, Johns Hopkins University, Baltimore. Pp. 146; various tables. Third edition, rewritten. Baltimore: By the Authors, 1933. Price, \$1.50.

THIS excellent volume, which presents in non-technical language the principles and applications of the modern science of nutrition, has been rewritten for a third edition.

E. W.

POSTURE. By FRANK D. DICKSON, M.D., Orthopedic Surgeon, Saint Luke's Hospital and the Kansas City General Hospital. Pp. 213; 118 illustrations. **ORTHOPEDICS IN CHILDHOOD.** By WILLIAM L. SNEED, M.D., Attending Surgeon, Hospital for the Relief of the Ruptured and Crippled, etc. Pp. 318; 145 illustrations. Philadelphia: J. B. Lippincott Company, 1931. Price, \$5.00 each.

BOTH of these volumes of the Everyday Practice Series, edited by Harlow Brooks, M.D., are written in a very simple style. The material is condensed and limited. Apparently no attempt is made to make either volume authoritative but rather to present the subjects in a manner slightly more expansive than a "compend." It is felt that both authors, probably at the instigation of the editor, have made the mistake of "writing down" to their readers. The illustrations are poorly reproduced and many are recognized as old friends. G. W.

BOOKS RECEIVED.

NEW BOOKS.

Bone Growth in Health and Disease. By H. A. HARRIS, D.Sc. (LOND.), M.B., B.S. (LOND.), B.Sc. (WALES), M.R.C.S., M.R.C.P., Professor of Clinical Anatomy, University College and University College Hospital, London; Hunterian Professor and Arris and Gale Lecturer of the Royal College of Surgeons, etc. Pp. 248; 201 illustrations. New York: Oxford University Press, 1933. Price, \$10.50.

The Science of Radiology. By various contributors. Edited by OTTO GLASSER, Cleveland Clinic Foundation. Pp. 450; 108 illustrations. Springfield, Ill.: Charles C Thomas, 1933. Price, \$4.50.

Great Men of Science. A History of Scientific Progress. By PHILIPP LENARD, formerly Professor of Physics and Director of the Radiological Institute in the University of Heidelberg; Nobel Laureate; Rumford Medallist of the Royal Society of London; Franklin Medallist of the Franklin Institute of Philadelphia. Translated from the Second German Edition by DR. H. STAFFORD HATFIELD. With a Preface by E. N. DAC. ANDRADE, Quain Professor of Physics in the University of London. Pp. 389; illustrated. New York: The Macmillan Company, 1933. Price, \$3.00.

Your Long-suffering Stomach. By ARTHUR F. KRAETZER, M.D. Pp. 120; illustrated. New York: Robert M. McBride & Co., 1933. Price, \$1.50.

The 1933 Year Book of Radiology. Diagnosis. Edited by CHARLES A. WATERS, M.D., Associate in Roentgenology, Johns Hopkins University; Assistant Visiting Roentgenologist, Johns Hopkins Hospital. Therapeutics. Edited by IRA I. KAPLAN, B.Sc., M.D., Director, Division of Cancer, Department of Hospitals, City of New York; Visiting Radiation Therapist, Bellevue Hospital, etc. Pp. 804; 780 illustrations. Chicago: The Year Book of Publishers, Inc., 1933. Price, \$7.00.

The Great Doctors. A Biological History of Medicine. By HENRY E. SIGERIST, Professor of the History of Medicine, The Johns Hopkins University. Translated by EDEN and CEDAR PAUL. Pp. 436; illustrated. New York: W. W. Norton & Co. Inc., 1933. Price, \$4.00.

The Absorption of Insulin from the Alimentary Tract in the Presence of Protein-phospholipin Compounds. By S. PESKIND, B.S., M.D. Pp. 19. Cleveland: The S. P. Mount Printing Company, 1931.

Some Modern Extensions of Beaumont's Studies on Alexis St. Martin. Beaumont Foundation Lectures. By W. B. CANNON, M.D., S. C., LL.D., George Higginson Professor of Physiology, Harvard Medical School, Beaumont Lecturer for 1933. Pp. 87. Detroit: Lectureship Foundation Committee of the Wayne County Medical Society, 1933.

Surgery of the Stomach and Duodenum. By J. SHELTON HORSLEY, M.D., F.A.C.S., LL.D., Attending Surgeon, St. Elizabeth's Hospital, Richmond, Va. Pp. 260; 136 illustrations. St. Louis: The C. V. Mosby Company, 1933. Price, \$7.50.

The Medical Clinics of North America, Volume 17, No. 2 (Chicago Number—September, 1933). Pp. 233; 36 illustrations. Philadelphia: W. B. Saunders Company, 1933.

NEW EDITIONS.

Infections of the Hand. By ALLEN B. KANAVAL, M.D., Sc.D., Professor of Surgery, Northwestern University Medical School, Chicago; Attending Surgeon, Wesley Memorial and Passavant Memorial Hospitals, Chicago. Pp. 552; 216 illustrations. Sixth Edition thoroughly revised. Philadelphia: Lea & Febiger, 1933. Price, \$6.00.

The Technic of Local Anesthesia. By ARTHUR E. HERTZLER, A.M., M.D., Ph.D., LL.D., F.A.C.S., Professor of Surgery in the University of Kansas; Surgeon to the Halstead Hospital, Halstead, Kan.; to the St. Luke's Hospital and St. Mary's Hospital, Kansas City, Mo., and to the Providence Hospital, Kansas City, Kan. Pp. 292; 148 illustrations. Fifth Edition. St. Louis: The C. V. Mosby Company, 1933. Price, \$5.00.

The Enlarged Prostate and Prostatic Obstruction. By KENNETH M. WALKER, F.R.C.S., M.A., M.B., B.C., Jacksonian Prizeman and Hunterian Professor, Royal College of Surgeons 1911, 1922, 1924, 1933; Lecturer in Venereal Diseases, St. Bartholomew's Hospital, etc. Pp. 223; 63 illustrations, 1 colored. Second Edition. New York: Oxford University Press, 1933. Price, \$4.25.

Food, Nutrition and Health. By E. V. MCCOLLUM, Ph.D., Sc.D., and J. ERNESTINE BECKER, M.A., Professor and Associate, of Biochemistry, School of Hygiene and Public Health, Johns Hopkins University, Baltimore. Pp. 146; various tables. Third Edition rewritten. Baltimore: By the Authors, 1933. Price, \$1.50. (Review, p. 874).

Pathogenic Microorganisms. By WILLIAM HALLOCK PARK, M.D., Professor of Bacteriology and Hygiene, University and Bellevue Hospital Medical College and Director of the Bureau of Laboratories of the Department of Health, New York City, and ANNA WESSELS WILLIAMS, M.D., Assistant Director of the Bureau of Laboratories of the Department of Health, New York City. Pp. 867; 215 engravings and 11 full-page plates. Tenth Edition, enlarged and thoroughly revised. Philadelphia: Lea & Febiger, 1933. Price, \$7.00.

Starling's Principles of Human Physiology. Sixth Edition, Edited and Revised by C. LOVATT EVANS, D.Sc., F.R.C.P., F.R.S., Jodrell Professor of Physiology in University College, London. The Chapters on the Central Nervous System and Sense Organs Revised by H. HARTRIDGE, M.A., M.D., Sc.D., F.R.S., Professor of Physiology at St. Bartholomew's Medical College. Pp. 1122; 562 illustrations, 10 in color. Philadelphia: Lea & Febiger, 1933. Price, \$8.75.

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The Blood in Cases of Unexplained Gastric Anacidity.—There have been many expressions of opinion published or expressed orally of the effect that those individuals who have an unexplained achlorhydria represent potential cases of pernicious anemia and that, while for a time at least, as in early life, this difficulty in the gastric secretion is entirely without harm to the individual, nevertheless ultimately many of them will develop a pernicious type of anemia. As POLLAND (*J. Clin. Invest.*, 1933, 12, 599) writes, there have been innumerable studies on those people who have pernicious anemia which show that they suffer from anacidity but on the other hand there has never been a comprehensive blood survey of the people who have this difficulty in their gastric secretion. He therefore studied a group of 26 males and 22 females who had an anacidity after an injection of histamin. Most of these patients did not have primarily digestive complaints. The duration of the anacidity was variable, extending from 1 to 56 months, with the average of the males 27 months and the females slightly over 19. Patients with such diseases as carcinoma, syphilis, chronic wasting and a few other diseases were excluded. The study included the complete blood count with platelet and reticulocyte estimations, the average diameter of the red corpuscle, and icterus indices and van den Bergh test. The detailed reports are presented in a series of tables. The hemoglobin content in the males averaged 87.6 per cent as contrasted with the control group whose hemoglobin percentage was 93.3; the grams per cent of the test group was 14.9 and the controls 16.07. The female test and control group was comparable to the male. The red cell count showed no striking difference in the two groups. Color indices were 0.9 or higher and the white cell counts were within normal range. The platelet count and the estimation of the number of reticulocytes also showed nothing of moment, whereas the icterus index and the van den Bergh were slightly above normal. The measurements of the red cells showed again nothing of significance. Polland points out that if the blood counts of the anacidity individuals are compared with the controls who have normal gastric secretion no significant differences appear and he concludes from these studies that there is no evidence to substantiate the idea that anacidity *in itself* leads to anemia.

SURGERY

UNDER THE CHARGE OF

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Total Thyroidectomy—A Therapeutic Measure in Congestive Heart Failure.—In February, 1933, ROSENBLUM and LEVINE (*Am. J. Med. Sci.*, 1933, 185, 219) reported a follow-up study of 69 "thyrocardiacs" in whom subtotal thyroidectomy was performed. The final conclusion in this paper was indeed interesting: "The occurrence of striking improvement following subtotal thyroidectomy in a patient with advanced congestive heart failure, in whom the thyroid gland was normal, suggests that this operation may be useful more generally in the treatment of various forms of cardiac disease."

The cardiac improvement that so frequently follows a subtotal thyroidectomy in patients with thyrotoxicosis and cardiac disease is a familiar clinical observation. BLUMGART, LEVINE and BERLIN (*Arch. Int. Med.*, 1933, 51, 866) and BLUMGART, RISEMAN, DAVIS and BERLIN (*Ibid.*, 1933, 52, 165) have demonstrated the close relationship that exists between the basal metabolic rate and the velocity of blood flow and thus between the tissue metabolism and the demands made upon the heart. In patients with metabolic rates of about +30, the velocity of the blood flow was found to be twice the normal while in myxedematous patients with low metabolic rates the velocity of the blood flow was at times only one-half the normal velocity. In congestive heart failure the velocity of the blood was found to be "considerably slower than in non-cardiac patients with a similar basal metabolic rate." As a logical outgrowth of their observations on this relationship was their suggestion that a lowering of the normal metabolic rate by removal of the thyroid gland in patients with congestive heart disease might enable the heart adequately to meet these decreased demands upon it and thus restore compensation. A subtotal thyroidectomy was performed on 2 patients who showed no evidence of disturbed thyroid function but who had severe congestive heart disease, and on 1 patient with angina pectoris but with an increased metabolic rate of +30. Definite improvement followed these operations but it was temporary in 2 of the patients, becoming less as their metabolic rates returned to normal after the first drop. It was then suggested that total thyroidectomy be done to insure a permanent lowering of the metabolic rate. One patient was subjected to this operation with a fall in his metabolic rate to -28 and marked improvement in his cardiac symptoms.

Total thyroidectomy is not an infrequent operation but in order to attain permanent results the thyroid tissue must be more completely removed than is usual in the so-called total thyroidectomy. BERLIN (*Am. J. Surg.*, 1933, 21, 173) points out that "shaving the posterior portion of each lateral lobe as close as possible to the capsule, or

stripping the capsule from the posterior surface of the lobe" (GILMAN and KAY, *Am. J. Med. Sci.*, 1928, 175, 350) is not sufficient. All thyroid tissue must be removed. The parathyroid glands must of course be carefully identified and guarded. Total thyroidectomy also involves the region of the external laryngeal and the recurrent laryngeal nerves, so great care must be exercised to avoid damage to these structures. Since the patients are not thyrotoxic they usually stand the operation surprisingly well. Berlin has reported the surgical technique of total ablation of the thyroid in a series of 11 cardiac patients and the precautions which must be observed. That this operation offers restoration of function to certain otherwise hopelessly incapacitated cardiac patients, at least for a time, seems probable.

As in all new radical procedures it is highly probable that the results obtained by BLUMGART and his associates (*Arch. Int. Med.*, 1933, 51, 866; 52, 165) may lead to many fatalities due to the improper selection of material and inexperience in thyroid surgery. The surgeon should not attempt to select the material but should, as BERLIN (*Am. J. Surg.*, 1933, 21, 173) has done, see that this is done by competent cardiologists.

THERAPEUTICS

UNDER THE CHARGE OF

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The Pharmacology and Therapeutic Action of a New Crystalline Digitalis Glucosid.—The active digitalis glucosids consist of a combination of a sugar component and of an aglucone. The aglucone part of the glucosid is pharmacologically less active and, in water, practically insoluble. It is through the addition of the sugar component that the glucosid becomes soluble in water, and thus the blood stream can carry it to the cardiac muscle. Today it is thought that the potency of the digitalis leaf depends mainly on the presence of three active glucosids—digitoxin, digitalin and digitalein. Whether these glucosids and other substances obtained from the galenic preparations are present as such in the digitalis leaf has never been proven. Willstätter and his associates have repeatedly demonstrated that the presence of enzymes in plants can change substances to be extracted from them. STOLL and KREIS (*München. med. Wchnschr.*, 1933, 80, 723), therefore, undertook the study of the chemistry of the digitalis leaf with the aid of a method which prevents enzyme action during extraction. Under such circumstances no digitoxin was obtained from the leaf of digitalis purpurea, but instead a glucosid called "purpurea glucoside A," which contains 1 molecule more glucose than digitoxin. A ferment in the

digitalis leaf called "digipurpidose" splits down the "purpurea glucoside A" into sugar and digitoxin. The authors also undertook the chemical study of *Digitalis lanata*, a species of foxglove common in Hungary, and particularly rich in glucosids. Using similar methods, the authors have isolated a crystalline glucosid called "digilanid." By using a method of separation with chloroform and methyl alcohol they have split this glucosid into three crystalline glucosids called "digilanid A, B and C." Each of these three glucosids consists of 3 sugar molecules, 3 molecules of digitoxose and 1 molecule of glucose, but the aglucone in each is different. It is digitoxigenin in digilanid A, gitoxigenin in digilanid B and digoxigenin in digilanid C. Digilanid is a glucosid with the highest sugar content known. Digilanid and its split products were tested in animals by ROTHLIN (*München. med. Wchnschr.*, 1933, 80, 726). The fatal dose of digilanid in cats is 0.34 mg. per kg. intravenously and 0.35 mg. subcutaneously. The fact that orally it is only half as toxic as by vein indicates good intestinal absorbability. They estimated that the muscle of the heart per kilogram takes up 27 times more glucosid than 1 kg. of average body weight. Various experiments described all indicated typical digitalis effect in animals. The therapeutic properties of "digilanid" were studied by HOCHREIN and LECHLEITNER (*München. med. Wchnschr.*, 1933, 80, 727). In using a solution, 1 cc. containing 0.5 mg. of the glucosid, usually 0.5 cc. (0.25 mg.), 3 times daily, induced beneficial digitalis effect in 5 to 10 days. An overdose induced typical digitalis intoxication. For a maintenance dose, 0.15 mg. once or twice daily sufficed. The beneficial effect was estimated with the aid of comparative measurements of pulse, respiration, venous pressure, diuresis, etc. The results indicated an improvement of the circulation in the majority of patients studied. The authors claim that the diuretic effect of digilanid was particularly prominent, and that prompt improvement followed the oral administration of this glucosid in severe cases treated heretofore by the intravenous administration of strophanthin. The authors recommend the use of digilanid.

(Abstractor.—While the above investigation seems to be important from point of view of digitalis chemistry, the therapeutic results do not give definite evidence that would indicate that for routine clinical use the administration of "digilanid" offers advantages over a standardized tincture or infusion of digitalis.)

PEDIATRICS

UNDER THE CHARGE OF
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Hereditary Gaucher's Disease.—ANDERSON (*J. Am. Med. Assn.*, 1933, 101, 979) defines Gaucher's disease as a non-hereditary congenital familial disease due to disturbed lipid metabolism with the production of an abnormal material called kersasin. This is stored by histiocytes of reticulo-endothelial origin, giving rise to the typical Gaucher cell,

which is found in all tissues, chiefly the spleen, lymph glands, liver and bone marrow. Clinically the disease is characterized by splenomegaly, hepatomegaly, pigmentation of the skin, pinguecula-like thickenings of the ocular conjunctivæ, hemorrhagic diathesis, unique changes in the bones with discrete or confluent rarefactions, leukopenia, anemia of the hypochromic type, thrombocytopenia, and in infants there may be a preponderance of neurologic symptoms. This report is the investigation into the history of a Russian family in which there is a possibility of hereditary transmission of this disease. There were 9 children in this family. The paternal grandmother died at the age of 22. She and two of her sisters had large abdomens and a yellowish-brown discoloration of the skin and died of a common cause. The son of this woman and the father of the patients died at the age of 55 of myocardial insufficiency, emphysema and chronic bronchitis. He was in the hospital twice, and the records show no evidence of enlargement of the spleen. He had 1 brother and 1 sister, but no history of these 2 individuals was available. The mother of the patients is living and has heart disease but no evidence of splenomegaly. Of the 9 children 3 are dead. One daughter died of measles at the age of $1\frac{1}{2}$ years; another died at 6. She had a large abdomen, and a pale greenish-yellow color. One daughter died when she was 17. She had a large abdomen, a brownish-yellow discoloration of the skin, and a large spleen that had been removed. There was much ascites and the peritoneum was studded with tubercles, but the pathologic report was Gaucher's spleen. Death occurred 3 months after the operation from extensive pulmonary tuberculosis. Three sons and 3 daughters survive. None of the sons show any splenic enlargement, skin discoloration or other signs of Gaucher's disease. One son has 4 children all apparently healthy; another 1 infant apparently healthy. All 3 of the living daughters have a pale yellowish-brown discoloration of the exposed skin and 2 of them have many acne pustules. One shows no signs of Gaucher's disease other than the color of her skin. Her spleen is not palpable. Another daughter has an enlarged spleen and although splenic puncture was not allowed Gaucher's disease is considered the cause of her condition. The third daughter, who is the eldest daughter living, has an enlarged spleen and by splenic puncture it has been proved to be Gaucher's disease. This last woman has 1 son and had 1 miscarriage. The living son has no evidence of Gaucher's disease. From the studies made in this report Gaucher's disease appears to manifest itself in females, but the transmission is through the male branches. As this is the only known report in the literature no definite conclusions can be made, but this should stimulate the reporting of other family histories where Gaucher's disease has been observed.

The Blood Picture in Icterus Neonatorum Familiaris Gravis and Its Diagnostic Significance.—ALTZITZOGLOU (*Monats. f. Kindhk.*, 1933, 58, 329) says that among the various forms of icterus in the newborn, icterus gravis is of especial importance because of its serious consequences for the family. The fact that a similar case has already occurred in the family, particularly if in the same generation, is of the greatest significance in the diagnosis. Isolated cases are possible, and it is important that the first case occurring in a family be recognized,

especially because an early diagnosis will make possible therapeutic measures which are often helpful in a condition that so frequently ends fatally. Erythroblastosis is a characteristic symptom of this disease. Since it is present physiologically in the newborn, it may be difficult to estimate this symptom unless it occurs in an extreme form. Erythroblastosis has a pathologic significance if it increases during the first few days of life. In doubtful cases it is advisable to count the normoblasts in addition to considering the history and the clinical symptoms. Early diagnosis is of extreme importance as it allows for early transfusion, which may cure this otherwise fatal disorder.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Operative Injury to the Ureters.—During the course of operations upon the pelvic organs there is always a possibility of injury to one or both ureters and while the reported incidence of this accident is less than 0.5 per cent it is probable that the accident occurs, frequently unrecognized, in a greater number of cases than reports would indicate. In discussing this subject NEWELL (*Am. J. Obst. and Gynec.*, 1933, 25, 220) reports 8 such cases and states that if a ligature is discovered on a ureter at the time of operation, the proper treatment is to deligate as soon as possible since the ligature is usually not sufficient to cause permanent injury. If the ureter has been severed, a uretero-ureteral anastomosis should be performed. Transplanting the ureter into the bladder is only fairly satisfactory, as the contraction of the wall of the bladder constricts the ureter, eventually causing a pyonephrosis and death of the kidney. If the patient is in poor condition and only one ureter is damaged, a ligation may be done, which will cause death of the kidney. If the ureter has been crushed by a clamp, the injury should be carefully examined and if it is determined to be severe, end to end anastomosis should be done in order to prevent a fistula. If both ureters have been ligated and this is not discovered until several days after operation the patient's condition is a serious one. The ideal treatment is deligation if the condition of the patient will warrant such a serious operation, but these patients are uremic and the operation is a tedious one. In general, therefore, nephrostomy as an immediate procedure is safer and when the patient's general condition has improved, the more extensive operation of deligation can be performed. The most common sequelæ of ureteral injuries are fistulas, which usually occur from 3 to 12 days after operation and may be either vaginal or abdominal, the former more common than the latter. Such fistulas occur when the ureter is severed either partially or completely, or the blood sup-

ply so injured by clamping that necrosis occurs, or as a result of stripping the ureter of its blood supply, followed by necrosis. Newell believes that it is best to wait from 1 to 6 months after the primary operation before attempting to cure the fistula because sometimes the scar tissue contraction which occurs will cause a spontaneous cure of the fistula although a hydronephrosis and death of the kidney will eventually result in most cases. He believes the best plan in dealing with these cases is to put the plain facts before the patient, stating the chance of failure if anastomosis is attempted and that it might be necessary to undergo a second operation for removal of the kidney. If the other kidney is normal and the patient desires it, a nephrectomy might be performed outright on the affected side and thus avoid the possibility of two serious operations.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Contribution on the Symptomatology and Diagnosis of Tumors of the Stalk of the Pituitary Gland from the Ocular Point of View.—SHIMKIN (*Ann. d'Ocul.*, 1933, 170, 127) reports 3 cases which illustrate different clinical syndromes produced by suprasellar tumors of the Rathke pouch cyst type. The first case showed pallor of the optic disks and bitemporal hemianopsia but had no symptoms of endocrine disturbance. Roentgenograms revealed enlargement of the sella and a calcified mass, 22 x 13 mm. in size, above the sella. In the second case, adiposogenital dystrophy and pituitary dwarfism were associated with bilateral choked disks, paralysis of the left external rectus and right facial palsy. Roentgenograms revealed a calcified mass, 11 x 8 mm. in size, above and partially in the sella and an otherwise normal sella. In the third case; adiposogenital dystrophy with cessation of menses was associated at first with pallor of the optic disks, bitemporal scotomata and bitemporal hemianopsia for colors. In 7 years, bilateral simple optic atrophy had developed with complete blindness on the left and temporal hemianopsia on the right, the central vision being reduced to counting fingers. The patient also developed glycosuria. Three years later the glycosuria had disappeared, menses had returned and the central vision of the right eye had returned to normal though a temporal hemianopsia remained. Roentgenograms showed enlargement of the sella with destruction of the anterior and posterior clinoids but no increase in the depth of the sella. The author interprets this case as one of a Rathke pouch cyst with spontaneous rupture since the patient received no treatment except novasurol and insulin. Roentgen therapy had no effect on the first case. Spinal puncture produced a decrease in the height of the choked disks and some improvement of vision in the second case. Unfortunately, none of the 3 cases was verified by surgery or necropsy.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Nasal Secretions. The Value of Cytologic Examination to the Rhinologist.—Attention has been drawn in recent years to the value of cytologic examination of nasal secretions in the diagnosis of diseases of the nose and accessory sinuses. LINDSAY and WALSH (*Arch. Otolaryngol.*, 1933, 17, 783) present the results of 100 routine examinations of nasal smears taken from patients with acute and chronic rhinitis and sinusitis. Smears were made by having the patient blow material from the nose onto a glass slide. This material was then spread as one spreads a blood smear. The smears were allowed to dry in the air and later were stained with Wright's stain. Few cells occurred in normal nasal secretions. The secretions in pathologic nasal conditions contained an abundance of cells. The presence of eosinophils in nasal secretions, the authors state, is indicative of vasomotor rhinitis. However, "no allergy was demonstrable in 14.9 per cent of the cases in which there was a high percentage of eosinophils in the nasal secretions." When vasomotor rhinitis was complicated by infection the ratio of eosinophils to neutrophils was lowered but in cases of infection without vasomotor rhinitis the eosinophil count in the nasal secretion was not higher than 1 per cent. In cases of allergic rhinitis, eosinophils were absent from the nasal secretions during quiescent periods. The number of eosinophils in the nasal secretions affords a simple and effective laboratory aid in the diagnosis of vasomotor rhinitis when the clinical signs of the condition are masked by those of a complicating infection.

Effect of Extract of the Suprarenal Cortex on Maxillary Sinusitis in the Rabbit.—WENNER (*Arch. Otolaryngol.*, 1933, 17, 774) studied the effect of extract of the suprarenal cortex on maxillary sinusitis, which he produced in 52 rabbits by irrigating the paranasal sinuses every 48 hours for 10 days with from 0.3 to 0.5 per cent solution of sodium alizarin sulphonate. When a nasal discharge appeared, the rabbits were divided into two groups. One was given 3 intramuscular injections of the extract of suprarenal cortex in doses of 0.5 cc. per kilogram of body weight over a period of 1 week. The second or control group received no extract. Both control and experimental animals were killed 17 days after the last sinus irrigation, and the antral mucosa was removed. On microscopic examination the antral mucosæ of the control rabbits showed a well-defined inflammatory reaction; whereas, no evidence of infection was noted in the antral linings of the animals receiving the suprarenal cortical extract, which produced a consistent decrease in hemoglobin, a change in alkali reserve, and an increased number of vacuoles in the cytoplasm of the cells of the suprarenal cortex.

RADIOLOGY

UNDER THE CHARGE OF

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Roentgen Findings in Splenomegaly.—The roentgenologic phenomena observed in 6 cases of splenomegaly, examined with the barium meal, are reported by HABBE (*Am. J. Roent. and Rad. Ther.*, 1933, 29, 449). In all of the cases there was a definite downward displacement of the splenic flexure to or below the level of the hepatic flexure, together with a variable degree of inward displacement. The stomach was displaced to the right in 3 cases, compressed posteriorly in 2 and neither displaced nor compressed in 1. In 2 cases the lower end of the esophagus was displaced to the right. In no instance was the left diaphragm displaced upward. The left kidney was localized in 3 cases, either by simple roentgenography or pyelography, and in 2 the kidney was displaced downward. In the remaining case the kidney was not depressed although the spleen was markedly enlarged.

Pathologic Changes in Diseases of Joints.—From a review of 120 specimens of resected joints GHORMLEY (*Am. J. Roent. and Rad. Ther.*, 1933, 29, 729) presents the pathologic picture of various common affections of the joints as related to the roentgenologic manifestations. He emphasizes the fact that often, so far as the roentgenogram is considered, the same lesion will appear entirely different at different stages. At certain stages diverse diseases may resemble each other, both pathologically and roentgenologically. For example, it seems heretical to speak of tuberculosis and proliferative arthritis in the same breath, yet the author describes numerous points of similarity in their morbid anatomy. He holds that the ideal time to make a diagnosis of disease of the joints is before lesions can be detected roentgenologically, but this is not often possible.

The Roentgen Findings in Suppuration of the Petrous Apex.—According to TAYLOR (*Am. J. Roent. and Rad. Therap.*, 1933, 30, 156) suppuration in the apical portion of the petrous pyramid (petrositis) is a complication of an acute otitic infection and can be recognized clinically and roentgenologically. Clinically it is characterized by (a) profuse otorrhea occurring after a period of cessation following simple mastoidectomy; (b) retro-orbital pain, along the distribution of the ophthalmic branch of the fifth nerve, and (c) sepsis. Roentgenologic manifestations are diminished aëration, deficient trabeculations, intense atrophy, perforation and finally destruction of the apical contour. These changes occur only in pneumatized petrous pyramids. Operative interference is indicated when both symptoms and roentgenologic signs are present. Cases with roentgenologic signs but without symptoms have adequate drainage, and, if not operated on, will probably terminate in a protracted otorrhea.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Hallucinations, Pseudohallucinations and Obsessions.—CLAUDE and EY (*Ann. Medico-Psychol.*, 1932, 90, 273) designates two orders of cases under obsession. The one, phobias, impulsions, certain "ideative" obsessions, characterized by their forced, incoercible character, he calls active obsessions. The others, characterized by their character xenopathy, are the obsessional parasitic phenomena which seem to constitute the majority of the symptoms designed as pseudohallucinations (hallucinoses, psychic pseudohallucinations, aperceptive representations, inspirations, etc.). As to the pathogenic interpretation, the anxiety states, the affective complexes appear to render count of the active obsessions. The passive or parasitic obsessions are too generally represented as always presented in the psychic by a mechanic automatic neoformation. The author attributes certain ones (paresthesias, real troubles of thought) to elementary cerebral excitations or globules, others to an affective mechanism analogous to that which goes with the constitution of the active obsessions (delirious anguish, affective rôle in the projection outside of self), still others to a state of low psychologic tension with properly psychasthenic mechanism. Psychasthenia appears as the fall of the capacities of mental synthesis, which maintain our psychic life under the authority of the voluntary activity. It produces a mental confusion which gives rise to some abnormal sentiments of strangeness, automatism, to the illusion that the elements of our psychic life no more belong to us. Regarded as a very general psychopathologic mechanism, the psychasthenia appears as a process, which, indifferent to the classification of psychiatry, finds itself again at the bottom of a series of pathologic states, in particular, mania, melancholia, dementia præcox and chronic delirium. If one accepts such an extension of the mechanism, it appears to apply itself as well to the active obsessions as to the parasitic. An analysis of the phenomena reveals the relative independence that the symptom, in its form and its content, presents relatively to its physiologic cause. The authors believe that the symptoms is subordinated indirectly to its physiologic condition without being entirely and immediately determined by it. In the mass of psychic facts there are two domains: the exterior world, the world of objects and of being; and the interior world, the field of our volitions. The hallucination presents itself to the consciousness of the subject as an objective reality. The pseudohallucinations pertain to the interior world. They appear to the consciousness of the patient who experiences them as phenomena without reality and which, however, are not produced by themselves. The

same as in the hallucinations there is an error, the product of a delusion. As to the same conditions of thought in this semiobjectivity, we see that they are realized by some different mechanisms, be it of affective projection, or by the lowering of the psychologic tension (psychasthenia). The last mechanism permits us to know there are in the conditioning of these phenomena not something more, but something less of it. That which is lacking is the capacity of mastering, of synthesizing our psychic activity, of feeling our unity and coherence.

Thrombosis of a Superior Cerebral Vein.—DAVIS (*J. Nerv. and Ment. Dis.*, 1933, 77, 122) presents a case of this unusual condition, 2 cases previously reported. Operative and necropsy findings confirmed the diagnosis. "According to MacCallum, the consensus of opinion is that the thrombosis is found by some mechanical obstruction or slowing of the stream of blood at a point where the endothelium is diseased or injured. Because of the operative procedure, we cannot be certain of the local pathology of the particular vessel in question but there was evidence of sclerotic changes in other vessels, such as the aorta, left coronary artery and adrenal vein. With the clinical history of an acute infection and a low blood pressure plus the pathologic findings of a passive congestion in the spleen and liver, there was sufficient evidence to indicate the presence of a venous stasis, which would, in turn, favor the production of a thrombosis."

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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A Serologic Differentiation of Human and Other Groups of Hemolytic Streptococci.—The classification of hemolytic streptococci by a precipitin reaction, as presented by LANCEFIELD (*J. Exp. Med.*, 1933, 57, 571) is based on the presence of a carbohydrate, a so-called C substance which is not type specific for *Streptococcus hæmolyticus*, but is characteristic for human strains. Antisera were obtained by immunizing rabbits with formolized broth cultures of the organisms. The extracts of the organisms were prepared by the addition of hydrochloric acid to a saline suspension of a young broth culture, the mixture heated to boiling for 10 minutes, cooled and centrifuged. The clear supernatant fluid or extract is used in a series of increasing amounts, with a constant volume of antiserum, incubated at 37° C. for 2 hours and kept in ice box overnight. One hundred and six strains of organisms were employed and could be divided into groups having a definite relation to their source. *Streptococcus viridans* was used as a control.

Group A was composed chiefly of strains of human origin; Group B chiefly of bovine origin, from mastitis and normal milk; Group C from various lower animals; Group D from cheese; Group E from certified milk. A striking correlation was found between the results of the serologic method and those based on biochemical and cultural tests used by other investigators, viz., final pH, hydrolysis of sodium hippurate, reduction of methylene blue milk, fermentation reactions and lysis by streptococcus bacteriophage. The group specific substance present in Group A is identified as carbohydrate in nature. The composition of the specific substances for the other groups has not been determined, but it seems likely that they belong to the class of carbohydrates, each being chemically distinct and serologically specific for the individual group.

Further Observations on the Cultivation of Vaccine Virus in Lifeless Media.—RIVERS and WARD (*J. Exp. Med.*, 1933, 57, 741) repeated the work of EAGLES and KORDI (*Proc. Roy. Soc. London, Series B*, 1932) in an attempt at verification of the statements of the latter that they could cultivate virus in a medium free from cells. They were entirely unsuccessful in ten attempts to show a multiplication of the virus on a cell-free media. They were able to demonstrate that the same virus could be grown in media containing bits of minced viable tissue. They concluded that in Eagles and Kordi's experiments, the preparation of tissues did not kill them, but left some cells not only viable, but capable of proliferation. Furthermore they concluded that the presence of viable cells in culture media is essential for the multiplication of vaccine virus.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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WASHINGTON, D. C.

Bacteriological Studies of a Milk-borne Outbreak of Scarlet Fever.—WELCH and MICKLE (*Am. J. Hyg.*, 1933, 17, 229) found that the organisms isolated from clinical cases of scarlet fever and sore throat in the outbreak studied gave the biologic and morphologic characteristics of *Streptococcus scarlatinae*. This classification was subsequently confirmed by serologic studies in another laboratory. Two milk handlers, operating a dairy definitely connected with the outbreak by epidemiologic data, harbored in their throats organisms identical in every respect with those isolated from the clinical cases. These studies indicate that the presence of a distinct capsule on a β -hemolytic streptococcus is not sufficient evidence that the organism is *S. epidemicus*.

without further studies on its colonial, biochemical and serologic properties. Evidence is also presented which indicates that the classification of streptococci on the basis of the type of lesion produced in the animal body is a questionable procedure. It is probable that the course of the infection is subject, in addition to the type of organism involved, to one or both of the following determining factors: (1) Fluctuation or variation in the virulence of different cultures of the same organism; (2) variation in the individual resistances of the experimental animals, whether due to environmental or hereditary causes.

The Maternity Ward of the General Hospital.—According to DELEE and SIEDENTOPF (*J. Am. Med. Assn.*, 1933, 100, 6), hospitalization of maternity cases is increasing everywhere, but the puerperal mortality is not decreasing anywhere. Numerous authors have called attention to the high institutional mortality compared with that of deliveries in the home. Meddlesome midwifery and puerperal infection, either singly or in combination, seem to cause the greater part of the mortality. More or less documented reports of 38 epidemics of puerperal infection, of which 35 were in the maternity wards of general hospitals, were collected by the present authors. They state that numerous authorities agree with them that women are safer from infection at home or in a specialized maternity building, and some go even further in their ideas of strictness of isolation. Meddlesome midwifery must be abated or made safe. Something is wrong with the maternity wards of general hospitals, and a great deal ought to be done about it. Architectural and administrative isolation of the clean maternity is recommended until more is known about the nature of puerperal infection.

The Pellagra-preventive Value of Various Foods.—WHEELER (*U. S. Pub. Health Rep.*, 1931, 46, 2663) found that canned spinach supplies the pellagra-preventive vitamin, but cannot be regarded as especially rich in it. It is, however, considered an important contributory source of this factor. Canned turnip greens supply the pellagra-preventive vitamin and, at least in liberal quantity, adequately supplement an otherwise pellagra-producing diet. This substance meets many of the requirements of a practical and effective dietary supplement in the pellagrous sections. The mature onion is a very poor source of the pellagra-preventive vitamin. Canned green beans are, relatively, a poor source of the pellagra-preventive vitamin. In a continuation of his studies (*Ibid.*, 1933, 48, 67) he reports that dried bakers' yeast is a good source of the pellagra-preventive factor, and its potency is retained after heating in the steam autoclave at 15 pounds' pressure for 7½ hours. Canned flaked haddock contains the pellagra-preventive factor but in an amount so small that a relatively large proportion is required adequately to supplement an otherwise pellagra-producing diet. Some less commonly observed symptoms associated with the use of an intermediate allowance of haddock are described and their significance is briefly discussed. Canned green peas supply the pellagra-preventive factor and may be found a highly practical and convenient source of this essential in the pellagrous sections during the spring months when pellagra-preventive supplements are scarcest.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF OCTOBER 16, 1933.

Galvanotaxis of Leukocytes.—MORTON McCUTCHEON and WILLIAM B. WARTMAN (Laboratory of Pathology, University of Pennsylvania). Emigration of leukocytes from bloodvessels in inflamed areas is generally attributed to chemotaxis or chemotropism. It is possible, however, that an electric factor plays a part. The hydrogen-ion concentration of inflamed areas is frequently increased, and such chemical changes would, according to Abramson, give rise to differences in electric potential sufficient to account for emigration of leukocytes. Conceivably an electric field might cause either passive transportation of leukocytes (electrophoresis) or it might determine merely the direction of a cell moving actively by its own amœboid movement (galvanotaxis). Experiments were made to find out whether leukocytes exhibit galvanotaxis, and if so, toward which pole they move. A drop of rabbit leukocyte suspension was allowed to spread between slide and coverslip. Under opposite edges of the coverslip extended strips of filter paper connecting with non-polarizable electrodes. The E. M. F. employed was 45 volts. When the cells were observed under the oil-immersion lens, spontaneous random amœboid movement was seen to begin after a few minutes. When the current was turned on, the direction of locomotion was not affected at first, though electrophoresis of suspended particles began immediately. After about 2 minutes the cell oriented itself in the electric field and moved toward the cathode. When the current was reversed the cell again required about 2 minutes before it once more moved toward the cathode. Under the microscope the streaming of the protoplasm, as evidenced by movements of the cell granules, showed that the cell was moving actively on the glass surface, that it was not being rolled along or otherwise transported by the electroösmotic stream. The mechanism of the reaction to the electric current, whether it consists in electric polarization of the cell, is uncertain. It is concluded that under these conditions, leukocytes show amœboid galvanotactic movement toward the cathode.

Recent Pharmacological Developments in the Study of Tissue Extracts.—J. C. MUNCH (Sharp & Dohme, Philadelphia).

The S-fraction of Tissue Extract and Its Possible Clinical Application.—J. B. WOLFFE (Sharp & Dohme, Philadelphia).

Experiences with Divinyl Ether.—S. GOLDSCHMIDT, I. S. RAVDIN and B. LUCKÉ (Laboratories of Physiology, Research Surgery and Pathology, University of Pennsylvania). In 1930 Leake and Chen predicted from a consideration of the chemo-pharmacological properties of diethyl ether and of ethylene that compounds combining the chemical properties of each would be of interest as general anesthetic agents. Such a compound would be divinyl ether. In 1931, Ruigh and Major reported the successful preparation of pure divinyl ether and described its properties.

The material which we have used has had added to it a small amount of absolute alcohol and an "inhibiting" substance.

In the dog the anesthetic concentration in jugular vein blood averaged 28 mg. per cent and the lethal concentration 68 mg. per cent. In man the anesthetic concentration in blood drawn from a vein in the antecubital fossa averaged 18 mg. per cent. The anesthetic was found to be four times as potent as diethyl ether. The "margin of safety" is as 1 to 2.4.

Liver necrosis occurred in well-fed dogs when the anesthetic was administered for a 3-hour period in 8 of 27 animals. In the *Macacus rhesus* monkey liver necrosis did not result even after 6 consecutive hours of anesthesia.

The effect on the blood pressure and respiration of the dog was similar to that produced by diethyl ether. Respiration failed before the circulation in both the dog and monkey.

The anesthetic has been administered for 758 general surgical operations in the Hospital of the University of Pennsylvania. Induction and recovery are rapid. Vomiting occurred in 9 per cent of the patients. No liver changes have been observed in man by us but two instances of liver necrosis have occurred at the Johns Hopkins Hospital.

It is too early to state the exact place which this anesthetic will have until the clinical experience is greater, but the present observations seem to indicate that it may prove to be a very useful substance.

Spectrophotometric Studies. (a) Hemochromogens and Related Compounds (b) A Technique for Examination of Undiluted Blood.

—DAVID L. DRABKIN and J. HAROLD AUSTIN (Departments of Physiological Chemistry and Research Medicine, University of Pennsylvania).

(a) Reduced hemin in alkaline solution combines with various nitrogenous substances to form reduced hemochromogens which have an exceedingly intense, narrow region of absorption in the green (the α band) and a less intense and broader absorption toward the blue end of the spectrum (the β band). Reduced hemochromogens are easily oxidized in air, yielding oxidized hemochromogens which also have characteristic spectra with the bands shifted toward the red and with a reversal in the strength of the α and β bands.

We have devoted most of our attention to the following derivatives: pyridin hemochromogen prepared by the addition of pyridin (final concentration 8 per cent) to reduced hemin in 0.01 N NaOH; globin hemochromogen prepared by the addition of NaOH (final concentration 0.01 N) to reduced hemoglobin; and the substances formed by the addition of pyridin to reduced hemoglobin or to oxyhemoglobin.

The last mentioned derivatives seem of especial interest. On the addition of pyridin to reduced hemoglobin a characteristic orange-red precipitate is formed when the concentration of pyridin is 8 per cent; upon further addition of pyridin to a concentration of 40 per cent the precipitate dissolves, yielding a solution with a characteristic reduced hemochromogen-like spectrum. This solution saturated in a tonometer with CO undergoes a change in color and the spectrum developed is very similar to, though not identical with, that characteristic of CO. Removal of CO by evacuation restores the original reduced hemochromogen-like spectrum. Upon exposure of the reduced pyridin hemoglobin solution to air the spectrum of the solution is immediately changed to

that of an oxidized hemochromogen. The latter spectrum is also obtained on the addition of sufficient pyridin to oxyhemoglobin; but in this case no precipitate forms. The addition of KCN to the solution oxidized in the air gives rise to a spectrum indistinguishable from that of cyanhemoglobin prepared from methemoglobin.

While the spectra of reduced and oxidized globin hemochromogen are in general similar to those obtained by adding pyridin to hemoglobin, we have not succeeded in producing either the CO derivative of the reduced hemochromogen or the cyanhemoglobin-like derivative of the oxidized globin hemochromogen. Oxidized globin hemochromogen on standing exposed to air undergoes a further change, yielding a spectrum very similar to the ill defined spectrum obtained on adding 0.1 N NaOH to methemoglobin. These findings suggest the interpretation that the reduced and oxidized derivatives produced by the addition of pyridin to hemoglobin are closer analogues of oxyhemoglobin and methemoglobin, respectively, than other hemochromogens thus far studied.

(b) We have designed a cell which permits the study of defibrinated or oxalated blood as drawn and without exposure to air or alteration by diluents not in gaseous equilibrium with the blood.

The chamber of the cell, ground out of a plate of optical glass, is 0.07 mm. in depth, and is readily filled and emptied by means of two glass capillary tubes, connected with the chamber by ground openings in a heavy plate glass cover, forming the floor of the chamber.

When saponized dog's blood is used, oxyhemoglobin and reduced hemoglobin yield, at various wave-lengths, extinction coefficients which, corrected for concentration and depth of solution, are almost identical with those obtained with 1 to 100 and 1 to 1000 dilutions of blood in 1 cm. and 10 cm. cells, respectively. Solutions of crystallized horse hemoglobin in concentrations as high as 42.6 gm. per 100 cc. have yielded spectrophotometric curves identical with those of oxyhemoglobin of dog's blood. This extends the range of validity of Beer's law for these pigments. Owing to turbidity, non-hemolyzed blood yields very different constants.

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